The use of Thalidomide as a treatment for cancer cachexia

Protocol for a randomised, double blinded, placebo controlled trial

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Titles, roles and contact details

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04/02/08 version 6
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Sponsor's Reference Number         220105v1
Portsmouth Hospitals Trust Research and Development Number         PHT/2005/02
EudraCT Number         2005-000371-18
ISRCTN Number         ISRCTN51456701
### Abbreviations and definitions

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<tr>
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<td>ADL</td>
<td>Activities of Daily Living</td>
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<td>ANOVA</td>
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<td>Enzyme-linked immunoabsorbent assay</td>
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<td>EORTC QLQ-C30</td>
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<td>Eicosapentaenoic acid</td>
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<td>NALIA</td>
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<td>NF-κB</td>
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<td>Proteolysis inducing factor</td>
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<td>TNF-α</td>
<td>Tumour necrosis factor alpha</td>
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Protocol Synopsis

Title
The use of Thalidomide as a treatment for cancer cachexia

Sponsor
None

Study design
Randomised, double blinded, placebo controlled trial

Primary objective
1. To evaluate the ability of Thalidomide to attenuate loss of weight loss in patients with cachexia associated with incurable upper gastrointestinal adenocarcinomas

Secondary objectives
1. To evaluate any impact on functional or overall quality of life
2. To assess safety and tolerability of Thalidomide in patients with incurable gastrointestinal adenocarcinomas
3. To evaluate any change in overall survival
4. To obtain serum and urinary profiles of factors previously implicated in the development of cachexia for both the control and treated group

Sites
Queen Alexandra Hospital, Portsmouth

Number of subjects
180

Eligibility criteria
Patients over the age of 18 years with incurable upper gastrointestinal adenocarcinomas, weight loss of over 1kg per month and able to give informed consent. Patients must be willing and able to adhere to the strict guidelines for use of Thalidomide (see appendix)

Drug dosage and administration
Thalidomide 200 mg or placebo given once daily at bedtime for 26 weeks

Procedures
Follow-up at weeks 0, 4, 8, 12 and 26 for evaluation of body mass index, lean body mass and quality of life. Blood and urine samples will be collected for routine haematology and biochemistry, along with measurement of levels of cachexia factors
Primary endpoint
Rate of clinical response as defined by attenuation of loss of lean body mass

Secondary endpoints
functional or overall quality of life
lean muscle mass
grip strength
overall survival from date of study entry
levels of cachexia factors
toxicity

Statistical considerations
The sample size to detect weight gain of 2kg at 4 weeks, assuming a between subject standard deviation of 4.3 (based on our previous study\textsuperscript{53}) with 80% power requires 74 subjects per treatment group. Inflating this by 20% to allow for attrition requires 90 subjects per group.

Analysis will be performed on an intention to treat basis. The difference in weight gain between groups will be compared using analysis of covariance to account for age, sex and site of primary. Both crude and adjusted estimates of the effect of Thalidomide will be presented, together with 95% confidence intervals and corresponding p values.

Analysis of survival data will be performed using a Cox proportional hazards regression model to account for treatment type, age, sex and site of primary.

Within the validated Quality of Life questionnaire EORTC QLQ-C30, the specific scales identified as key components for this study are those of physical functional and role functional scores (questions numbered 1-5 and 6-7 respectively. The entire questionnaire will be analysed for discussion. All scores will be analysed using analysis of variance (ANOVA) and only survivors will be analysed at each time point.
1. Background

1.1 Cachexia
Cachexia can be defined as a state of general ill health characterised by malnutrition, weakness and emaciation occurring during the course of a chronic disease\(^1\). It is common in patients with cancers, in particular those of upper gastrointestinal origin. Of those with gastric or pancreatic cancer, cachexia is seen in over 80%\(^2\), with a third losing greater than 10% of their pre-morbid weight. Cancer cachexia is a major cause of morbidity and mortality, contributing to death in up to one in five cases\(^3\). The amount of weight lost, and the rapidity with which it is lost, correlates inversely to survival, with death commonly occurring when the individual's weight has dropped to 70% of previous levels\(^4\).

There are significant differences in cachexia associated weight loss compared with that seen in starvation. In starvation the major loss tends be from adipose tissue and that protein which is lost is divided equally between skeletal and visceral muscle. In cachexia weight is lost preferentially from the skeletal muscle compartments with relative sparing of visceral proteins and adipose tissue. In fact, the liver often enlarges in cachexia due to production of acute phase proteins. The loss of skeletal muscle leads to difficulty in carrying out normal activities, often reducing independence. In gastrointestinal cancer patients, weight loss of 2.5kg over a 6 to 8 week period is enough to cause significant deterioration in performance status\(^5\).

Cachexia cannot be explained solely by the reduced appetite and food intake of many cancer patients, nor can it be reversed with nutritional supplements or appetite stimulants alone\(^6\)\(^7\). It seems the anorexia is an effect rather than a main cause of cachexia\(^8\) and is probably mediated at least partly by circulating leptin (anorexigenic), gherlin (orexigenic) and hypothalamic neuropeptide Y (orexigenic). The only nutritional supplement that has been shown to be of benefit in experimental models is eicosapentaenoic acid (EPA)\(^9\) and the benefits are yet to be proven in human studies\(^10\).

The mechanisms involved are not fully understood but various tumour products and cytokines have been implicated. Recently identified catabolic products produced by tumour cells include lipid mobilising factor (LMF), leukaemia inhibiting factor (LIF) and proteolysis inducing factor (PIF). It has been shown that PIF is produced specifically by those tumours associated with weight loss\(^11\)\(^12\) and in one study was detectable in the urine of gastrointestinal cancer patients only at times of weight loss\(^13\). PIF isolated from human urine induces cachexia when administered to mice\(^11\).

The cytokines thought to mediate cachexia are produced both by the tumour itself and by the host response to the tumour. Cytokines implicated by experimental models are interleukin 1\(\beta\) (IL-1\(\beta\)) interleukin 6 (IL-6)\(^14\)\(^15\), interferon \(\gamma\) (IFN\(\gamma\))\(^16\)\(^17\) and tumour necrosis factor \(\alpha\) (TNF\(\alpha\))\(^17\)\(^20\) but human data is scanty. TNF\(\alpha\) is produced by several different cell types in response to bacterial toxins, inflammatory products and other invasive stimuli. Nude mice
inoculated with TNFα producing tumour cells have been shown to become increasing wasted and die more rapidly than a control group inoculated with non-TNFα secreting tumour cells\textsuperscript{21}. Continuous administration of TNFα to animals results in dose-dependent anorexia, lean body wasting and death\textsuperscript{22}.

PIF, IL-1β and TNF-α all increase levels of a nuclear transcription factor named nuclear factor κB (NF-κB) that induces gene expression of many cytokines, is involved in apoptosis and oncogenesis and controls the ubiquitin-proteosome proteolytic pathway\textsuperscript{23}. There are three major pathways of protein catabolism in skeletal muscle, but only the ubiquitin-proteosome proteolytic pathway involves breakdown of myofibrillar proteins and is therefore the most important pathway in cachexia. NF-κB exists as a trimer in cytoplasm, bound to DNA binding proteins and an inhibitory protein IκB\textsuperscript{24}. Inducible IκB kinases (IKKs) phosphorylate IκB so causing its destruction, leaving an active NF-κB dimer capable of translocation to the nucleus and regulation of gene expression\textsuperscript{25}. PIF induces NF-κB via arachidonic acid production from myotubules. TNF-α and IL-1β increase IKK activity so inducing NF-κB through destruction of IκB\textsuperscript{26}.

1.2 Measurement of lean body mass
One of the major obstacles into cachexia research has been measurement of lean body mass. There are accurate techniques available, for example underwater weighing or isotope dilution but all involve expensive or bulky equipment are not practical outside a laboratory research setting. Anthropometric techniques such as measurement of weight, triceps skin fold thickness, midarm circumference are simple and validated but have an average error of around 7-8%\textsuperscript{27}. Dual-energy x-ray absorptometry (DEXA) scanning uses X-rays of two energy levels that are attenuated by different tissues to different extents to offer a precise and non-invasive method which makes no assumptions of the chemical constancy of lean tissue mass\textsuperscript{28,29,30}. It is however expensive, involves a small radiation dose and necessitates immobile equipment. Bio-impedance is a widely used but relatively new technology that relies on mathematical equations validated in specific patient groups to determine body composition data from raw bio-impedance values. The bio-impedance value is largely influenced by the type of tissue the current is travelling through (eg fat, water, muscle) but will also be influenced by other factors such as extracellular water and cell membrane integrity. Bio-impedance is relatively cheap, portable, easy to use and safe. Equations have been validated in many varying patient groups but not specifically for cachexic patients who will have inevitable changes in electrolyte composition, body water compartmentalisation and cell membrane integrity\textsuperscript{31,32}.

1.3 Thalidomide
Thalidomide was originally marketed in 1956 as a sedative, relaxant and anti-emetic for pregnancy associated nausea. It was however withdrawn from the European market in 1961 following a relatively high incidence of previously rare limb abnormalities in children born to women who had taken the drug, even in very small amounts, during their pregnancies. During this time the US
Food and Drug Administration (FDA) did not approve it due to concerns over long term side effects.

In 1965 it re-emerged as a treatment for erythema nodosum leprosum (ENL)\(^{33,34}\), a painful, vasculitic complication of leprosy, gaining FDA approval for this indication in 1998. During these last three decades the only noted major side effect for the non-pregnant patient has been an infrequent peripheral neuropathy which occurred in 3 out of 49 patients treated for six months in one study\(^{35}\) and in 1 out of 23 patients in another\(^{36}\). Thalidomide derivatives are currently being developed which may further reduce side effects.

Renewed interest was stimulated in 1991 by the discovery of Thalidomide’s powerful suppression of TNF-\(\alpha\) activity\(^{37}\), exerting its effects by enhancing degradation of its mRNA\(^{38,39}\). Subsequent work has shown Thalidomide to modulate several other factors including IFN-\(\gamma\), IL-10, IL-12, cyclo-oxygenase 2 (COX-2). It also blocks TNF-\(\alpha\) and IL-1\(\beta\) activation of NF-\(\kappa\)B\(^{26}\). This is at least partially the basis for its (now well documented) immunomodulatory and anti-inflammatory properties\(^{40,41}\). Recent studies have found Thalidomide to be effective in the management of a wide variety of clinical conditions, including HIV associated wasting\(^{42}\) and the weight loss experienced in pulmonary tuberculosis\(^{43}\).

There has recently been a great deal of interest in the use of anti-angiogenic agents as adjuncts to standard chemotherapy in both haematological and solid organ malignancies. Bevacizumab (a humanised monoclonal antibody directed against vascular endothelial growth factor) was the first angiogenesis inhibitor to market after it was given US FDA approval for use as a first-line treatment for patients with metastatic colorectal cancer in 2004. The anti-angiogenic potential of Thalidomide led to trials into its use as an anti-cancer agent, many of which are ongoing. At present, few phase III trials have been completed but preliminary data suggests a benefit in multiple myeloma\(^{44}\), refractory Waldenström’s macroglobulinaemia\(^{45}\), myelodysplasia\(^{46}\), advanced prostate cancer\(^{47}\), renal-cell carcinoma\(^{48}\), high-grade glioma\(^{49}\), melanoma\(^{50}\) and colorectal cancer\(^{51}\), in some instances resulting in reduction of tumour bulk. Thalidomide is approved in some countries for the treatment of multiple myeloma after the failure of standard therapies and the acute treatment of cutaneous manifestations of moderate to severe ENL. It has been shown that the response rate in multiple myeloma cannot be explained only by the reduction of angiogenesis\(^{52}\). It is possible that some of the anti-tumour effect is mediated by Thalidomide’s inactivation of NF-\(\kappa\)B, which is known to activate the expression of genes involved in cell growth and suppression of apoptosis\(^{26,53}\). Thalidomide also reduces production of Cox-2\(^{54}\), which is thought to play an important role in cancer therapy through angiogenesis, immune surveillance and apoptosis\(^{55}\). In metastatic, chemotherapy resistant colon cancer, the addition of Thalidomide to irinotecan chemotherapy improved response rates from 12-21% to 29%. Thalidomide’s sedative and anti-emetic effects also allowed patients improved toleration of the irinotecan\(^{56}\). Phase III studies are currently in progress.
1.4 Previous studies
To date there are only three published papers evaluating the use of Thalidomide in cancer cachexia. In the first, Bruera\textsuperscript{57} showed in an uncontrolled study involving 37 patients with terminal malignancy that Thalidomide’s anti-emetic, analgesic, and sedative properties were effective in the palliation of otherwise intractable symptoms in patients with terminal malignancy. More recently Khan et al.\textsuperscript{58} have reported an open label pilot study of Thalidomide in the treatment of cachexia in eleven patients with inoperable oesophageal cancer. In this study Thalidomide reversed weight loss over the two week period of the trial, and this was associated with an increase in lean body mass.

We have recently published the results of the first randomised placebo controlled trial of Thalidomide in the treatment of cancer cachexia\textsuperscript{59}. In this study we demonstrated that Thalidomide is safe and effective in attenuating weight loss in patients with cachexia secondary to advanced pancreatic cancer. In this study 50 patients were recruited to either Thalidomide (200mg per day) or placebo. Of these 33 patients (17 Thalidomide, 16 placebo) were available for assessment at four weeks and (12 Thalidomide, 8 placebo) at eight weeks. At four weeks, those who received Thalidomide had gained on average 0.37 kg in weight and 1.0 cm\textsuperscript{3} in arm muscle mass (AMA) compared with a loss of 2.21 kg (absolute difference 22.59 kg [95% confidence interval (CI) 24.3 to 20.8]; \( p = 0.005 \)) and 4.46 cm\textsuperscript{3} (absolute difference 25.6 cm\textsuperscript{3} [95% CI 28.9 to 22.2]; \( p = 0.002 \)) in the placebo group. At eight weeks, patients in the Thalidomide group had lost 0.06 kg in weight and 0.5 cm\textsuperscript{3} in AMA compared with a loss of 3.62 kg (absolute difference 23.57 kg [95% CI 26.8 to 20.3]; \( p = 0.034 \)) and 8.4 cm\textsuperscript{3} (absolute difference 27.9 cm\textsuperscript{3} [95% CI 214.0 to 21.8]; \( p = 0.014 \)) in the placebo group. Improvement in physical functioning correlated positively with weight gain \( (r = 0.56, p = 0.001) \).

Change in weight in pancreatic cancer patients randomized to either Thalidomide \((n=17\;\text{week 4}, \; n=12\; \text{week 8})\) or placebo \((n=16\; \text{week 4}, \; n=8\; \text{week 8})\); between groups \( p=0.005 \) at 4 weeks, and 0.034 at 8 weeks
The general weight loss correlated with a reduction in loss of lean body mass as measured by anthropometric techniques. There was also a trend towards prolonged life expectancy with a median survival of 148 days in the Thalidomide group compared to 110 days in the placebo group. This survival benefit is similar to that seen in recent trials using gemcitabine as single agent chemotherapy.

The Thalidomide was well tolerated; two patients (9%) complained of peripheral neuropathy that resolved on stopping the drug, and two patients (9%) developed a rash that necessitated withdrawing from the trial. A further four patients (17%) complained of severe daytime somnolence that required a reduction in drug dosage in two patients, and cessation of the drug in the other two. Conversely, those in the placebo arm suffered significantly more from insomnia (p=0.023). Constipation was the only other side effect experienced to significant levels (p=0.04). Further studies are required to investigate whether it is possible to generalise these results to cancer cachexia caused by other cancers, and whether there is a true survival benefit. There is also a lack of human data on the underlying biological processes of this condition and the affect Thalidomide has on these.
1 Aims and objectives

2.1 Hypothesis
Based on our previous work we hypothesise that Thalidomide can attenuate or reverse both total weight loss and loss of lean body mass in the cachexia associated with incurable upper gastrointestinal adenocarcinomas.

In addition we wish to investigate whether this is associated with an improved quality of life or survival benefit; to obtain a profile of the serum and urinary factors implicated in the development of cachexia and how these are affected by Thalidomide and to obtain a safety profile for Thalidomide in this patient group.

2.2 Objectives
Primary objectives
To evaluate the ability of Thalidomide, as compared to a placebo, to attenuate loss of weight in patients with incurable upper gastrointestinal adenocarcinomas.

Secondary objectives
1. To assess any impact on functional or overall quality of life
2. To calculate any change in overall survival.
3. To calculate any change in lean muscle mass
4. To calculate any change in grip strength
5. To obtain serum and urinary profiles of factors previously implicated in the development of cachexia for both the control and treated group
6. To document the safety and tolerability of Thalidomide in patients with incurable upper gastrointestinal adenocarcinomas.
3. Study Design

3.1 Trial type
This will be a non-commercial, NHS sponsored double-blind, placebo controlled clinical trial. A placebo has been chosen for the control group as there is no currently accepted standard or effective treatment for cachexia. Each subject will participate in the trial for a six month period.

3.2 Schedule of events

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3.3 Initial visit
At the initial visit the patient will be consented into the trial. They will then be allocated a trial identification number (1-180) by the drug manufacturing company. A case report form will be completed with the following data.

- Age
- Sex
- Race
- Pre-morbid weight and duration of weight loss (self documented or from patient notes if available)
- Concurrent and previous medical conditions
- Full drug history including over the counter medications and nutritional supplements
- Allergies
- Smoking history
- Alcohol intake
- All subjects will be asked specifically about symptoms over the past four weeks from a pre-established list reflecting the known side-effects of Thalidomide and based on CTCAE descriptions (appendix 10.1)
- Other symptoms over the last four weeks will be documented using CTCAE descriptions

Examination data with measurement of:

- Pulse
- Blood pressure
- Weight (measured without shoes and wearing light clothing only)
- Mid upper arm circumference (MAC) will be measured using stretch resistant tape
- Triceps skin-fold thickness (TSF) will be measured using Harpenden skinfold callipers
  - Bone free arm muscle area (AMA), a validated marker of lean muscle mass, will then be calculated from MAC and TSF using the formula $(MAC - \pi TSF)^2 / 4\pi$ minus a correction factor of 10 for male sex or 6.5 for female sex$^{20}$.
- Grip strength of the non-dominant hand using a digital hand grip dynamometer.
- Lean body mass using bioimpedance analysis (a quick and painless procedure in which bioimpedance is measured by electrodes attached to the body).
- Sensation to pinprick, light touch, vibration and proprioception.

Blood and urine samples be taken and analysed for:

- Full blood count
- Urea and electrolytes
- Liver function tests
- Thyroid function tests
- Markers of nutrition (e.g. albumin) and inflammation (e.g. c-reactive protein)
- Cytokine and tumour factor estimation (blood will be taken and stored in ice until centrifuged and then frozen at -80°C within two hours of
collection. All samples taken at peripheral sites will be transported in dry ice in batches to the Queen Alexandra Hospital where processing will take place) Commercially available ELISA kits will be used for cytokine measurement.
- Dr Michael Tisdale (Pharmaceutical Sciences Institute, Aston University Birmingham) has kindly agreed to supply monoclonal antibody to PIF.
- Presence of cytokine and cytokine receptor gene polymorphisms.

All female patients under the age of 54, and those over 54 but still menstruating, will have a urinary pregnancy test.
All subjects will be asked to complete a quality of life questionnaire (EORTC QLQ-C30 Version 3 – see appendix 10.2).
All subjects will be given an opportunity to see a dietician for general nutritional advice.

3.4 Subsequent visits
At weeks 4, 8, 12 and 26 height, weight, anthropometric measures and bioimpedance will be recorded on case report forms. At each visit subjects will be asked to complete a quality of life questionnaire and questioned about any symptoms, both in general terms (documented using CTCAE descriptions including severity grade) and from a pre-established list reflecting the known side effects of Thalidomide and based on CTCAE descriptions (see appendix 10.1). Any new symptoms will be explored with details concerning time of onset, action taken and outcome. At weeks 4, 8, 12 and 26 blood and urine tests will be repeated for measurement of full blood count, urea, electrolytes, liver function tests, cytokine and tumour factor measurement. If patients feel well enough they may be asked to have a DEXA scan. We have only limited access to the DEXA scanner and therefore whether a patient has a scan will depend upon whether the scanner is available and whether the patient feels strong enough to have a further test at that particular appointment. They will be asked to bring any unused medication to each appointment and questioned about their compliance since the previous visit. One month after completion of the medication, all participants will be contacted by telephone and questioned about any new symptoms. Any further follow up necessary will be organised through the general gastroenterology clinics. All women of childbearing potential will be required to have a monthly negative pregnancy test until one month following completion of the study.

Any patient developing symptoms or signs of peripheral neuropathy or neutropenia with less than 500 cells/mm³ will be immediately withdrawn from the trial. Any patient requiring chemotherapy or radiotherapy after trial enrolment will be withdrawn from the study. No patient will be replaced.

After six months patient survival will continue to be monitored using the hospital computer system.

3.5 End of Trial
The end of the trial will be defined by the last phone call to the last patient.
4 Endpoints

Primary endpoint
Weight change at four weeks.

Secondary endpoints
- functional or overall quality of life
- overall survival from date of study entry
- lean muscle mass
- grip strength
- serum and urinary levels of cachexia factors
- toxicity

5 Trial interventions

Each subject will receive Thalidomide 200mg (a dose based on that used for our previous study) or identical placebo once daily at bedtime for a period of 26 weeks. Thalidomide is prepared in capsules of 50mg, this will therefore entail taking four capsules per day. Patients will be asked to take one capsule on the first day and then increase by 50mg each day until on the full 200mg. If side effects are troublesome to the patient and not easily controlled by conventional means (e.g. anti-emetics or laxatives) then the dose will be reduced to 100mg, if they continue then the drug will be stopped.

Both Thalidomide and placebo will be manufactured by Penn Pharmaceuticals Services limited, Tredegar, Gwent NP22 3AA and supplied free of charge by Pharmion Ltd, Riverside House, Riverside Walk, Windsor, Berkshire SL4 1NA.

The drug will be supplied in 28 capsule blister packs labelled with the contact details of the co-ordinating investigator and ‘for clinical trial use only’. Enough drug for each subject for the six month course of the trial will be boxed and labelled from 1-180 to correspond to individual patient trial numbers. All supplies will be held in the Queen Alexandra Hospital Pharmacy until a patient is randomised into the study, at which point their individual supply will be transferred to their hospital and stored in that pharmacy. At each visit patients will be supplied with enough capsules from their allocated box to last until their next appointment. Patients will be asked to return any surplus drug and this will be disposed of through the hospital pharmacy. Shelf-life will exceed the two year trial period.

We are able to continue to supply Thalidomide after the trial for patients who wish to continue to take it. Only after careful discussion with each individual
patient with consideration of potential long-term side effects (peripheral neuropathy in particular) will this be considered.

Full details of Thalidomide’s international licensing are contained in the Investigator’s Brochure.

Subjects will, during the trial, continue to take any drug they are already taking although if using megesterol acetate or eicosapentaenoic acid they will need be losing the required amount of weight despite this in order to be included and they will be asked to remain on the same constant dose through the course of the trial.
6 Subjects

6.1 Subject selection
Patients with histological or cytological diagnosis of adenocarcinoma of the oesophagus, stomach, small bowel, ampulla or pancreas and no curative options will be eligible for inclusion in the study. Patients with pancreatic cancer diagnosed unequivocally by radiological and clinical means can be included without biopsy confirmation.

A total of 180 subjects will be recruited from The Queen Alexandra Hospital, Portsmouth, The North Hampshire Hospital, Basingstoke and the Royal Hampshire County Hospital, Winchester. We aim to recruit this number of patients over a two year period. If recruitment is slower than predicted then the trial will be opened to other local sites with the support of the NCRN.

6.2 Inclusion criteria
- Have a histological or cytological diagnosis of upper gastrointestinal (oesophagus, stomach, small bowel, ampulla or pancreas) adenocarcinoma. Patients with pancreatic cancer diagnosed unequivocally by radiological and clinical means can be included without biopsy confirmation.
- Have no curative options available which are acceptable to the patient.
- Have lost 5% total of pre-morbid body weight or be actively losing at least 1kg per month. Weight loss may be self-reported or obtained from previous documentation.
  - If a patient is using megestrol acetate (Megace, Megestrol) or eicosapentaenoic acid (Maxepa, Omacor, Prosure) and has been on a stable dose for at least a month but losing weight at the stated rate despite this they may be included. They will be asked to continue on this same dose for the course of the study.
  - Those using corticosteroids, non-steroidal anti-inflammatory drugs and other nutritional supplements or complementary therapies will not be restricted, the doses used will be recorded at each clinic visit.
- Have a predicted survival of at least 8 weeks.
- Aged over 18 years at the time to entry into the trial.
- Able to understand the information given and to give written informed consent.
- Able to take oral medications.
- Agree to the conditions of use of Thalidomide as enumerated (see appendix).
- Women who have not had their ovaries of uterus removed or who have been post-menopausal for at least two years, must have a negative urinary pregnancy test and negative pregnancy tests repeated on a monthly basis until one month after completion of the trial.
6.3 **Exclusion criteria**

- Unable to provide informed consent
- Involved in any other trial during the study period
- Received chemotherapy or radiotherapy within the previous four weeks
- Expected to receive chemotherapy or radiotherapy in the following six months
- Using varying doses of megesterol acetate or eicosapentaenoic acid
- Clinically detectable ascites or oedema
- Unable to take oral medication
- Pregnant or breast feeding
- Unable or considered unlikely to avoid pregnancy
- Evidence of peripheral neuropathy, severe constipation, vertigo or vestibular disease
- Previous adverse reaction to Thalidomide
- Any condition judged by the investigator to make the patient unsuitable for inclusion into the study due to interference with absorption of the drug or the overall interpretation of the data

6.4 **Subject recruitment**

Potential subjects will be identified from medical, surgical and oncology clinics. They must meet all of the inclusion criteria and none of the exclusion criteria. They will not be paid for their participation but will be reimbursed reasonable travel expenses for their clinic visits.

Copies of the patient information leaflet will be available in oncology and gastroenterology clinics. If a patient is eligible for the trial and interested in participating then they will be given a copy of the leaflet to read and their contact details passed on to the co-ordinating investigator. They will then be contacted by the co-ordinating investigator, given the opportunity to ask any questions and an initial visit will be arranged (in some instances it may be possible to arrange the initial visit to follow on from the patient’s original clinic appointment).

Written consent will be taken at the initial visit by either the co-ordinating or principle investigators or by the research nurse. All initial visits will be undertaken within NHS hospitals with NHS interpreters available for non-English speakers.

6.5 **Randomisation**

Subjects will be equally randomised in blocks of four to receive either treatment with Thalidomide or identical placebo once daily for a period of 26 weeks.

Stratification will be applied for pancreatic / non-pancreatic tumour origin.
The manufacturer of both the Thalidomide and the placebo tablets (Penn Pharmaceuticals) will carry out the randomisation procedure and un-blinding procedures. All participants, investigators and assessors will therefore be blinded until the end of the study.

7 Data recording

Data from the clinic visits will be recorded by the research nurses on case report forms. Both paper and electronic versions of the case report forms will be kept. Data will be entered electronically where a computer is available and a paper printout kept in the patient’s file. Paper copies will also be available for situations where access to a computer is difficult (e.g. home visits) to be filled in by hand. Data will then be transferred at the earliest opportunity into electronic format and the original handwritten form kept in the patient’s file. The database has been created using Microsoft Access.

Each patient will also have an individual case file. This will contain a signed consent forms, patient contact details and individual case report forms. The subject’s name will be recorded only on the subject contact details sheet. Any other study document will be identifiable through individual subject trial identification numbers, hospital numbers and dates of birth. The individual case files will be stored in a secure location within the individual participating hospitals. Electronic data will be stored using Microsoft access on only password protected computers and will be copied onto compact discs quarterly for backup and transfer to the chief investigator’s master database. These compact discs will be held securely at the Queen Alexandra Hospital.

Study documents (paper and electronic) will be retained for 15 years in a secure location.

Blood samples will be frozen and stored for 15 years in The Queen Alexandra pathology laboratory. It is anticipated that they will be used for further cytokine measurements in the future.

Data will be held on record in accordance with the Data Protection Act 1998 and will be handled in accordance with Caldicott Principles.

All trial related documents will be made available on request for monitoring and audit by the sponsor, Southampton research ethics committee B and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensing bodies.

8 Statistical analysis

The sample size to detect a 2kg difference in weight change between the two groups at 4 weeks, assuming a between subject standard deviation of 4.3 (based on our previous study\textsuperscript{53}) with 80% power requires 74 subjects per
treatment group. Inflating this by 20% to allow for attrition requires 90 subjects per group. The difference in weight will be compared using the unpaired t test.

Analysis will be performed on an intention to treat basis. The difference in weight gain between groups will be compared using analysis of covariance to account for age, sex and site of primary. Both crude and adjusted estimates of the effect of Thalidomide will be presented, together with 95% confidence intervals and corresponding p values.

Analysis of survival data will be performed using a Cox proportional hazards regression model to account for treatment type, age, sex and site of primary.

Within the validated Quality of Life questionnaire EORTC-C30, the specific scales identified as key components for this study are those of physical functional and role functional scores (questions numbered 1-5 and 6-7 respectively. The entire questionnaire will be analysed for discussion. All scores will be analysed using analysis of variance (ANOVA) and only survivors will be analysed at each time point.

9 Safety assessments

9.1 Adverse Events
An adverse event will be defined as any untoward medical occurrence in a patient / subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. This will include symptoms, signs (on clinical examination or on laboratory tests) and medical conditions, whether or not felt to be related to the study drug. Symptoms, signs and conditions present before starting the study drug will only be considered adverse events if they worsen after starting the study drug. Abnormal laboratory values or test results will only generally be considered adverse events if they induce clinical signs or symptoms or require intervention.

All new symptoms will be recorded at each clinic visit using both in general terms (documented using CTCAE descriptions including severity grade) and from a pre-established list reflecting the known side effects of Thalidomide and based on CTCAE descriptions (see appendix 10.1).

All adverse events will be described by:
1. duration (start and end dates),
2. severity grade (grade 1 – 5, as defined by the CTCAE - Appendix 10.2),
3. action(s) taken
4. outcome

Adverse event documentation from all sites will be collected and tabulated by the co-ordinating investigator on a quarterly basis. This information will be
9.2 Serious Adverse Events
A serious adverse event will be defined as an event that is:

- Results in death
- Is life threatening
- Results in persistent or significant or disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation.
- Results in a congenital abnormality or birth defect.

All patients involved in this study are terminally unwell and will therefore be expected to suffer a high rate of deaths, disability or hospitalisation during the course of the trial. These events will therefore only be considered Suspected Unexpected Serious Adverse Reactions (SUSARs) if the patient’s clinician (either general practitioner, hospital doctor or study staff) considers it abnormal within the patient’s disease process.

Any serious adverse event occurring after a patient receives study medication and for a period up to four weeks after stopping study drug will be reported by the principle investigator to the sponsor using a Portsmouth Hospitals Trust Serious Event Reporting Form within 3 calendar days of the event being discovered. They will submit a full report of the incident within 7 calendar days.

9.3 Interim analysis and monitoring
Every three months the co-ordinating investigator collect and correlate all case report forms for all sites. The results will be presented along with details of trial progress to a Trial Management Committee who will include the principle investigator for the Queen Alexandra Hospital, a consultant histopathologist, a representative of the sponsor, a statistician and a pharmacist. The details of these meeting will be minuted and sent to principle investigators from other sites, members of the Independent Data Monitoring Committee and any other relevant parties. Any concerns will be raised immediately with the IDMC. These meeting will form the basis of the quarterly sponsor’s safety report.

The Independent Data Monitoring Committee will include an independent consultant physician, an independent oncologist and independent statistician. This group will receive quarterly reports from the co-ordinating investigator and will meet formally on an annual basis. This group may request for the study to be un-blinded to them at any point.

Any adverse events occurring more commonly than would be expected will be investigated. If expected serious adverse events are found to be occurring at a rate higher than expected this will be reported immediately to the sponsor using a Portsmouth Hospitals Trust SUSAR form.
9.4 Teratogenesis precautions

There is a high risk of severe teratogenesis (malformation of the foetus) following first trimester (up to 13 weeks) exposure of the foetus to Thalidomide. The risks of teratogenesis following male exposure to Thalidomide are uncertain.

Women who are under the age of 54 years* (and are therefore considered to have childbearing potential) or men whose partners are such, and have not had a hysterectomy, must agree to use two forms of effective contraception at the same time, of which one must be the male condom. This must continue until at least one month after the final dose of Thalidomide for women, or three months for men. Female sterilisation and vasectomy are not 100% reliable on their own and thus a condom must also be used.

Women will need to have a negative urinary pregnancy test prior to starting the trial and should start the study drug during menstruation if pre-menopausal. The pregnancy test will be repeated monthly throughout the trial.

[* if the woman is aged 54 or over, but is still having natural periods or if her periods finished less than one year ago, then she should use contraception as described above]

Any patient who cannot avoid the chance of pregnancy may not take part in this trial.

10 Ethical conduct, governance and publication policy

The study will be performed subject to the approval of the Southampton Research Ethics Committee B, including site specific assessment.

The study will be conducted in accordance with:
- The Medicine for Human Use (Clinical Trial) regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care
- Declaration of Helsinki 1964

Results of the study will be published in peer-reviewed journals

11 Funding and Sponsorship

Funding has been secured from the Moulton Charitable trust. The Pharmion Corporation has agreed to supply both Thalidomide and identical lactose
based placebo capsules free of charge. Portsmouth Hospitals NHS Trust will act as sponsor for the trial.

12 Translational work

12.1 Measurement of cytokines using NALIA
This study will use the ELISA technique to measure cytokine and tumour factor levels. Multiple Nanodot Luminometric Immunoassays (NALIA) are a newer technology which allows bulk measurement of cytokines using a similar technique. It may be that we have the opportunity to incorporate some work with this new technique into the cytokine measurements for this study but will continue to substantiate our results with standard ELISAs until proper validation is possible.

12.3 IL-6 and fatigue
It has been shown that IL-6 is induces fatigue in healthy patients. When given to healthy runners in low dose it caused a significant impairment in performance. They also reported feeling depressed, tired and complained of heavy legs\textsuperscript{55}. Anti-IL-6 receptor monoclonal antibodies improve debilitating fatigue in patients with chronic inflammatory disorders\textsuperscript{56} but there is little research on IL-6 in cancer-related fatigue. We intend to examine correlations between IL-6 levels, IL-6 gene polymorphisms and fatigue as measured by the Quality of Life questionnaire.
### 13 Appendices

#### 13.1 Pre-established symptoms list

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory neuropathy</td>
<td>Asymptomatic; loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function</td>
<td>Sensory alteration or paraesthesia (including tingling), interfering with function, but not interfering with ADL</td>
<td>Sensory alteration or paraesthesia interfering with ADL</td>
<td>Disabling</td>
<td>Death</td>
</tr>
<tr>
<td>Neurpathic pain</td>
<td>Mild pain not interfering with function</td>
<td>Moderate pain; pain or analgesics interfering with function, but not interfering with ADL</td>
<td>Severe pain; pain or analgesics severely interfering with ADL</td>
<td>Disabling</td>
<td>-</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>Asymptomatic, weakness on exam / testing only</td>
<td>Symptomatic weakness interfering with function, but not interfering with ADL</td>
<td>Weakness interfering with ADL; bracing or assistance to walk (eg can or walker) indicated</td>
<td>Life-threatening; disabling (eg paralysis)</td>
<td>Death</td>
</tr>
<tr>
<td>Somnolence / depressed level of consciousness</td>
<td>-</td>
<td>Somnolence or sedation interfering with function, but not interfering with ADL</td>
<td>Obtundation or stupor; difficult to arouse; interfering with ADL</td>
<td>Coma</td>
<td>Death</td>
</tr>
<tr>
<td>Constipation</td>
<td>Occasional or intermittent symptoms, occasional use of stool softeners, laxatives, dietary modification, or enema</td>
<td>Persistent symptoms with regular use of laxatives or enemas indicated</td>
<td>Symptoms interfering with ADL; obstipation with manual evacuation indicated</td>
<td>Life-threatening consequences (eg obstruction, toxic megacolon)</td>
<td>Death</td>
</tr>
<tr>
<td>Rash</td>
<td>Macular or papular eruption or erythema without associated symptoms</td>
<td>Macular or popular eruption or erythema with pruritus or other associated symptoms; localised desquamation or other lesions covering &gt; 50% of body surface area</td>
<td>Severe, generalised erythroderma or macular, papular or vesicular eruption; desquamation covering &gt; 50% of body surface area</td>
<td>Generalised exfoliative, ulcerative or bullous dermatitis</td>
<td>Death</td>
</tr>
<tr>
<td>Pruritus / itching</td>
<td>Mild or localised</td>
<td>Intense or widespread</td>
<td>Intense or widespread and interfering with ADL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dry skin</td>
<td>Asymptomatic</td>
<td>Symptomatic, not interfering with ADL</td>
<td>Interfering with ADL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vasovagal episode</td>
<td>-</td>
<td>Present without loss of consciousness</td>
<td>Present with loss of consciousness</td>
<td>Life-threatening consequences</td>
<td>Death</td>
</tr>
<tr>
<td>Seizure</td>
<td>-</td>
<td>One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL</td>
<td>Seizures in which consciousness is not altered; poorly controlled seizure disorder, with breakthrough generalised seizures despite medical intervention</td>
<td>Seizures of any kind which are prolonged, repetitive, or difficult to control (eg status epilepticus, intractable epilepsy)</td>
<td>Death</td>
</tr>
<tr>
<td>Limb oedema</td>
<td>5-10% inter-limb discrepancy in volume or circumference at the point of greatest visible difference; swelling or obscuration of anatomical architecture on close inspection; pitting oedema</td>
<td>&gt;10-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomical architecture; obliteration of skin folds; readily apparent deviation from normal anatomical contour</td>
<td>&gt;30% inter-limb discrepancy in volume; lymphorrhoea; gross deviation from normal anatomical contour; interfering with ADL</td>
<td>Progression to malignancy (ie lymphangiosarcoma); amputation indicated; disabling</td>
<td>Death</td>
</tr>
</tbody>
</table>
13.2 Quality of Life questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ________________________________
Your birthdate (Day, Month, Year): ____________
Today's date (Day, Month, Year): ____________

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Bit</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Bit</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please go on to the next page
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>23. Did you feel irritable?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?  
    1 2 3 4 5 6 7  
    Very poor  Excellent

30. How would you rate your overall quality of life during the past week? 
    1 2 3 4 5 6 7  
    Very poor  Excellent

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13.3 Patient information

Study into the use of Thalidomide in the treatment of the weight loss and weakness experienced with gastrointestinal cancers

Summary

We are running a research study which we would like to invite you to participate in.

The purpose of the study is to find out whether the drug Thalidomide is useful in preventing the weight loss and weakness often seen in people with tumours of the digestive tract, and whether it may improve people’s life expectancy.

It is the same drug as the one that was used in pregnant women in the 1950s and caused deformities in their children. Since then it has been used for a wide variety of different conditions and has been shown that any side effects are normally minimal outside pregnancy.

We ran a study last year with people who had tumours of the pancreas and Thalidomide reversed the weight loss and seemed to increase the life expectancy, although the difference was not enough to be conclusive as there were only a small number of patients. In our study there was no change in people’s general well being, but in some other studies using Thalidomide for other similar conditions it has generally improved the way people feel.

We are now running a larger study, and including all tumours of the upper digestive tract and pancreas to try to establish for sure whether Thalidomide is helpful in this setting.

If you decide to take part, the study will involve five clinic visits over six months. At these visits you will be asked some questions, have a general examination and be asked for a blood and urine sample.

You will be given four capsules to take every night that may be Thalidomide or may be a placebo (inactive / dummy) tablet. Nobody will know which you are taking until the end of the trial.

If you decide not to participate this will not affect the treatment you receive in any way. However, if you feel you may wish to participate, we would be grateful if you would take some time to read through the details in the following pages.

The doctor co-ordinating the trial will then contact you over the next few days to answer any questions you may have and to organise your first visit.
RESEARCH SUBJECT INFORMATION AND INFORMED CONSENT

1. **Protocol title:** A randomised, double blinded, placebo controlled trial of the use of Thalidomide as a treatment for cancer cachexia

**Simplified title:** The use of Thalidomide in the treatment of the weight loss and weakness experienced with upper gastrointestinal adenocarcinomas

**Investigators:** Dr S R Green, Prof I A Cree, Dr P M Goggin

2. **Introduction**

You are being invited to participate in a research study. Before you decide whether to, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. You will be contacted within the next few days by the hospital doctor co-ordinating the trial who will be able to answer any questions you may have. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether you would like to take part.

Consumer for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and you'. This leaflet gives more information about medical research and looks at some questions you may want to ask. You may obtain copies from CERES, PO box 1365, London N16 OBW.

Thank you for reading this.

3. **What is the purpose of this study?**

People who have a tumour affecting their gastrointestinal (digestive) system often lose large amounts of weight during the course of their illness. This is very common and caused at least partly by the tumour itself rather than just a lack of appetite.

The trial is designed to find out whether the drug Thalidomide is helpful in controlling the symptoms of tumours affecting the digestive system and preventing this weight loss. It is already being used to treat some conditions including certain blood cancers and has been shown to be helpful in preventing the weight loss associated with AIDS and TB. It is not known exactly how Thalidomide works, but some of its effects are thought to be due to it reducing levels of chemicals called cytokines, which are produced by the body to help cells interact with each other in order to attack abnormal cells and infections. You may have heard of Thalidomide from when it was used in the 1950s as a sleeping tablet and anti-sickness tablet for pregnant women. Side effects for the women taking the drug were minimal but many of their babies were born with shortened limbs. For this reason strict precautions are now in place to ensure that nobody taking Thalidomide becomes pregnant.
There is some evidence that Thalidomide may be beneficial in preventing the weight loss and weakness experienced by patients with certain incurable tumours. In this trial we hope to prove the benefits of Thalidomide in similar tumours arising from different parts of the body. The trial will run for a six month period for each person.

4. **Why have I been chosen?**
You have been found to have a tumour of your gastrointestinal (digestive) system, and have experienced a certain amount of weight loss. The purpose of this study is to find out whether adding Thalidomide to any other treatments you may be using is useful, either by preventing further weight loss, improving quality of life or by prolonging survival. Approximately 180 patients from Portsmouth and the surrounding area will take part in the study.

5. **Do I have to take part?**
It is up to you whether you decide to take part in this study. Your participation is entirely voluntary. If you do decide to take part you will be given the information sheet to keep and be asked to sign a consent form. However you are still free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive from your hospital doctor. If you should decide to withdraw, you should contact the study team to discuss your treatment. If you decide to leave this study after taking the drug (or placebo) then you will be asked to return for a final visit as per the study schedule in section 6 for an end of study / early termination visit. These tests are performed for your safety and to protect you from any unexpected side effects.

The study doctor may stop the study medication at any time and you may be asked to leave the trial without your consent. You may be asked to leave the study if you do not follow directions or if the study shows signs of causing you harm. The study may be stopped at any time.

6. **What will happen to me if I take part?**
If you agree to take part in this study then you will participate for approximately 26 weeks (6 months). There will be a total of five clinic appointments, the longest of which will take approximately 45 minutes. Reasonable travel expenses will be paid for these visits. The schedule of the visits will be as follows:

**Telephone contact**
If you feel you may want to participate in the study and would like to find out more about it then your details will be passed to the doctor co-ordinating the study who will contact you within the next few days. This is an opportunity for you to ask any questions you may have. If after this phone call you would like to take part then an outpatient visit will be organised for you.
First visit
You will have another opportunity to ask any questions you may have thought of and then you will be asked to sign the two consent forms attached. One of these concerns participating in the trial, and the other concerns taking Thalidomide. You will receive a general health check from the study doctor. This will involve some questions about the history of your illness, your general health and which other medications you are currently taking; these will be similar to questions you would expect to be asked at any normal clinic appointment. A general physical examination will include measurement of your height, weight, the size of your arm, temperature, pulse and blood pressure and how accurate your sense of touch is. A ‘bioimpedance’ measurement will be taken. This is quick, painless way of measuring the various body constituents (e.g. fat, muscle, water). The actual procedure involves sticking electrodes onto the skin in a similar way to ECG recordings (heart traces). You will be asked to give a blood sample (approximately 10ml or two teaspoons of blood taken with a needle from your arm) and a urine sample. You will be asked to complete a questionnaire about how you are feeling in yourself and whether you are feeling unwell in any way.

You will then be ‘randomised’ into the study and given the study medication. Randomisation is like flipping a coin. Nobody, including you, your doctor, and the study staff, will know whether you have been given Thalidomide capsules or placebo (dummy / inactive) capsules. In the case of an emergency, or at the end of the trial, there is a computer system, which can be used to find out which tablet you have been taking. You will have a 50:50 (or one in two) chance of receiving Thalidomide and the same chance of receiving the placebo capsules.

You will receive your study medication along with instructions for taking the medication. It is important to take the medication as directed by the study staff.

Follow-up appointments
You will be asked to return after one month, two months and three months - a total of four further visits. At each visit you will be asked to bring any left over medication and used blister packs. You will be asked whether you may have been experiencing any side effects of the medication, and to repeat the questionnaire that you filled in at the first visit about how you are feeling in yourself. The general physical examination will be repeated and urine pregnancy test will be repeated on a monthly basis if you are a woman who is capable of bearing children. A further blood and urine sample will be requested at the one, three and six month visits. You will be given enough medication to last until your next visit.

End of study visit / early termination visit
After six months, or at any time that you wish to leave the study for any reason, you will be asked to come in for one final visit, which will be similar to the other follow-up appointments and include a final blood and urine test.
One month later you will receive a phone call, just to check you have not
developed any side effects after stopping the drug. Any women capable of
bearing children will be asked to have one last pregnancy test at this time.

If at the end of the trial it is found that you have been taking Thalidomide and
you have gained benefit from it, it may be possible for us to continue to supply
Thalidomide for you after the six months of the trial are over.

7. What do I have to do?
There are no restrictions to your normal life associated with taking part in the
study other than the necessity of avoiding pregnancy and complying with the
clinic visits as described above. If you are taking Megace, Megestrol, Maxepa,
Omacor or Prosure you will be asked not to alter the dose of these
medications during the course of the trial. If you require chemotherapy or
radiotherapy during the six months of the trial then it will be necessary to
withdraw from the trial. Thalidomide can occasionally make people feel
drowsy (although this is unusual if it is taken before bedtime). If you do feel
drowsy you should not drive or operate machinery. You can otherwise
continue your usual life including drinking moderate amounts of alcohol and
taking any other tablets you would normally take.

8. What is the drug being tested?
Thalidomide was originally used in the 1950s as an anti-sickness and
sleeping tablet, mainly for pregnant women. Unfortunately it was found to
cause deformities in the newborn children of these women. It was immediately
banned, but over the years it has become clear that, for non-pregnant people,
it is a well tolerated drug and that side effects are usually manageable. It has
been used in the treatment of many different diseases and has had approval
from the United States Food and Drug Administration (FDA) for the treatment
of some complications of leprosy since 1998.

We are hoping that it will prevent the weight loss often encountered by people
with tumours of the digestive tract, and help them to feel generally better in
themselves. In our earlier study there was a tendency for people taking the
drug to survive longer, although it was not possible to prove that this was an
effect of the drug.

9. What are the alternatives for diagnosis or treatment?
There are many different anti-cancer drugs available, and a wide variety of
drugs available to deal with most unpleasant symptoms people can
experience (e.g. sickness or pain). However there is no standard treatment for
the weight loss and weakness that people with digestive tract tumours often
experience, and it is not possible to prevent this with diet alone. For this
reason we are using a placebo (inactive / dummy) tablet to compare with
Thalidomide in this study.

The placebo tablet is necessary to ensure any effect is due to the drug and
not due to chance. To do this we have to compare the group of people taking
the drug with a similar group who are not taking the drug. You will have a
50:50 chance of getting either tablet.
You will be given a card (similar in size to a credit card) with details of the trial and emergency contact numbers. Please carry this with you at all times.

10. What are the side effects from receiving treatment when taking part?
All drugs may cause side effects and when using a new drug it is important for us to monitor for them.

**Pregnancy precautions**

*Nobody who is pregnant or who cannot avoid the chance of becoming pregnant can take part in this trial.*

There is a high risk of severe malformations to a baby if the mother is exposed to Thalidomide in the first 13 weeks of her pregnancy. The risk of birth defects following male exposure to Thalidomide, and the subsequent effects on their semen and sperm, are uncertain. Therefore any woman who becomes pregnant with a man who is taking Thalidomide is also potentially at high risk of having an affected baby.

Women capable of bearing children, or their partners, must use strict precautions to prevent pregnancy, until at least three months after stopping the study drug.

All women are considered to be of child bearing potential unless:
- her ovaries or uterus have been removed (hysterectomy)
- she has been post-menopausal for over 2 years

All men are considered capable of bearing children unless his testicles have been removed.

If you and your partner are able to have children, the only certain way to prevent pregnancy is to abstain from intercourse. If you are able to have children, you must agree to use at least TWO of the following birth control methods (double barrier method) at the same time: condom, vasectomy, tubal ligation (female sterilisation), vaginal diaphragm, IUD, sponge with spermicide and hormonal contraceptives (pills or implants).

Spermicides alone, and withdrawal, are not considered effective means of contraception. Neither female sterilisation, nor male vasectomy, is 100% reliable and therefore an additional form of contraception must be used. These contraceptive measures must be continued for the duration of the trial and three months after the final dose of the study drug for women. Similarly men should not donate semen while taking the study drug or for until at least three months after stopping it.

All women able to bear children will need to have a negative urinary pregnancy test prior to starting the trial, which will be repeated monthly throughout the trial. Female patients should neither breastfeed, nor use breast milk during the study or for at least three months afterwards.
Other side effects
The other main side effects that Thalidomide can cause are:
1. Damage to the nerves in the hands and the feet. This can take the form of pins and needles or weakness and if you notice it occurring you must contact us. If damage to the nerves does occur it is possible for it to be permanent though in most cases it is likely that there will be slow recovery.
2. Skin rash, that can occasionally be serious, so if it occurs you must contact us.
3. Drowsiness, that is not normally a problem if the tablet is taken before bed.
5. Loss or gain in appetite.
6. Dizziness.
7. Changes in the amount of hormone produced by the thyroid gland (this will be checked on the blood tests).

We will ask you to fill in a form at each visit to monitor for side effects and for you to report any unusual symptoms to us.
Nobody should donate blood while taking the study drug or for three months after stopping.

11. What are the benefits of taking part?
Participating in the study may or may not prevent the weight loss and weakness seen commonly in people with digestive tract tumours; it may or may not lengthen or improve the quality of your life. No guarantee can be made. It is possible that you may feel worse, or your life may be shortened by participating in the trial. The information collected from this study may help people with similar problems in the future.

12. What if new information becomes available?
Sometimes during the course of a research project, significant new information becomes available about the drug that is being studied. If this happens, the study staff will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw then your ongoing treatment will not be affected; if you decide to continue you may be asked to sign an updated consent form. On receiving new information the study staff might consider it in your best interests to withdraw you from the study, in which case they will explain their reasons to you.

13. What happens when the research study stops?
If you have been taking Thalidomide during the study and have gained a particular benefit from doing so, it may be possible for us to continue providing it for you after the study has finished. However, this cannot be guaranteed.

14. What if something goes wrong?
If you are harmed by taking part in this research project, the usual NHS indemnity procedures will apply. If you are harmed due to someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.
15. Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. We will inform your GP of your participation in this study.

16. What will happen to the results of the research study?
In the event that results of this study are given to medical journals, a code number will identify you. You will not be identified by name. If the results of this study are published, you may request a copy of the document from the study staff.

When all the study results are analysed, you may request to be informed which drug group you were assigned to (i.e. whether you were taking thalidomide or placebo).

17. Who is organising and funding the research?
This is a non-commercial NHS study based at Portsmouth Hospital. The study is being financed by a local charity which supports research likely to be of direct benefit to patients. A drug company called Pharmion will provide study medication. All clinic visits and procedures related to this study will be provided to you at no cost. Reasonable travel expenses will be reimbursed for your travel to and from clinic visits. You will not be paid for your participation in this study.

18. Who has reviewed this study?
The Southampton and South West Hampshire Research Ethics Committee B has given its approval to this study.

29. Who to contact for further information?
You are welcome to ask questions about the study at any time. If you have any questions regarding the research procedures please contact Tim Johns on telephone number 02392 286000 ext 5470.

For questions about your rights as a research subject please contact Patient Advice and Liaison Service on telephone number 02392 866295 or the Information Commissioner telephone number 01625 545745 or access www.dataprotection.gov.uk.

Thank you for taking the time to read this information.
13.4 Trial consent form - all patients

Consent form

Title of project: A randomised double blinded placebo controlled trial of Thalidomide in the treatment of incurable gastrointestinal cancers.

Name of Trial Co-ordinator Dr S R Green

Please initial boxes:
1. I confirm that I have read and understood the information sheet dated 04/02/08 version 6 for the above study and have had the opportunity to ask any questions.

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

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

4. I understand that the blood samples taken during the course of the trial will be stored for up to 15 years. They may be used in the future for research into conditions relating to cancer or weight loss and potential benefits thereof. They may also be used for unrelated work.

5. I agree to take part in the above study.

Name of Patient ______________________ Date ______________ Signature ______________________

Name of practitioner taking consent ______________________ Date ______________ Signature ______________________

04/02/08 version 6
13.5 Thalidomide Consent form – part a - all patients

Patient’s Initials  ---------  Date of Birth  ----/----/----
Sex:    (Male/Female)  Trial ID  ----------

The dose is …….mg. The tablets should be taken once a day, at bedtime

Please initial the following statements to signify that you have understood them completely:

Nerve problems. I understand that Thalidomide can cause nerve damage. I will report any tingling in my hands and feet to the study staff straight away. Once the Thalidomide has been stopped it is likely that any damage will repair itself but occasionally damage can be permanent……………………………..

Drowsiness. Thalidomide can occasionally make people feel drowsy during the day. If this is the case then I will not drive or operate machinery. Using alcohol or other sedatives can make the drowsiness worse…………………

Blood problems. Thalidomide can reduce the levels of white blood cells which may leave me more prone to infections and may change the amount of hormone produced by the thyroid gland. The white blood cells and thyroid hormone levels will be monitored with the regular blood tests but I will report any infections to the study staff………………………………………………………

Rash. Rashes can be serious. I will report these to the study staff………………

Other side effects. Other side effects of Thalidomide include: mood changes, dizziness, headaches, constipation, itching, ankle swelling, increased appetite, palpitations, blood clots, dry mouth and nausea. I agree to report any of these symptoms or anything unusual to the study staff……………………………………

Safety. I am responsible for keeping their tablets securely away from children and other adults. I will not share my tablets with others……………………
I will not donate blood or sperm while taking the study drug or for three months after stopping…………………………………………………………

If you have any questions or concerns while taking the study drug please contact Mr Tim Johns on 02392 286000 extension 5470

I have fully understood the above statements and realise understand that I can ask questions at any time. I give my informed consent to being treated with Thalidomide. I understand the risks inherent in treatment and the side effects that may occur. I understand that my consent precludes me from bringing any legal action against the doctor, hospital, clinic, pharmacy or Thalidomide’s manufacturer’s or suppliers in respect of any side effect and consequences of treatment for which the risk has been made known to me, both verbally and in this information sheet.

Patient’s signature……………………………………………..Date……………………
Practitioner’s signature……………………………………..Date……………………

04/02/08 version 6
**Thalidomide Consent form – part b - women of child bearing potential and their partners only**

Patient’s Initials  ---------  Date of Birth  ----/----/-----
Sex:  (Male/Female)  Trial ID  --------------

The dose is .......mg. The tablets should be taken once a day, at bedtime

Please initial the following statements to signify that you have understood them completely:

Thalidomide is highly toxic to the unborn child...........................................

I agree to use at least two highly effective forms of contraception at the same time while taking the study drug and for at least three months after stopping the drug. I understand that these methods include condom, vasectomy, tubal ligation (female sterilisation), vaginal diaphragm, IUD, sponge with spermicide and hormonal contraceptives (pills or implants) and that spermicides alone, and withdrawal, are not considered effective means of contraception.............

I agree to contact the study staff immediately if contraception fails or if a menstruation (period) is delayed.........................................................

**Women only**
I will to start the course of the study drug during menstruation (a period)........

I agree to monthly urinary pregnancy tests during treatment with the study drug and one month after stopping..........................................................

I agree that I will not breast feed while taking the study drug or for three months after stopping.................................................................

If contraception should fail and I become pregnant I agree to discuss termination of the pregnancy with my doctor...........................................

If you have any questions or concerns while taking the study drug please contact Mr Tim Johns on 02392 286000 extension 5470

I have fully understood the above statements and realise understand that I can ask questions at any time. I give my informed consent to being treated with Thalidomide. I understand the risks inherent in treatment and the side effects that may occur. I understand that my consent precludes me from bringing any legal action against the doctor, hospital, clinic, pharmacy or Thalidomide’s manufacturer’s or suppliers in respect of any side effect and consequences of treatment for which the risk has been made known to me, both verbally and in this information sheet.

Patient’s signature..................................................Date.............

Practitioner’s signature.............................................Date.............
13.6 *Dexa Scan Patient information sheet*

During the course of this trial you may be asked whether you would be willing to have an additional scan called a DEXA scan. DEXA stands for 'Dual Energy X-ray Absorptiometry'. These scans are usually used to look at thinning of bones (osteoporosis) but can also be used to give a highly accurate picture of the amount of fat, muscle and other tissues contained in the body.

The scan involves lying on a couch while an X-ray detector is positioned over the body. X-rays are then released from a machine under the couch towards the detector.

Different amount of X-ray will be absorbed depending on how much fat, muscle, bone and water a body contains. You will receive an X-ray dose from this test but it is small. You would need twenty of these tests to give you the same dose as a chest X-ray. To put it in perspective this is less than each of us is exposed to every day from natural radiation from the sun and soil. The test takes less than 10 minutes.

It is not possible to do this test for every patient at every appointment as it is expensive to do and the equipment is immobile. But by obtaining a small number of scans we will be able to ensure that the measurements we attain by other methods (eg. weighing, measuring skin fold thickness, bio-impedance) are giving us accurate answers.

The scan itself is quick and painless but any extra test will inevitably require more time and energy on your part. You should therefore not feel pressured into agreeing if you are asked to have a scan. Your participation in the trial will be equally valuable whether or not you have this extra test. If for any reason you would be interested in having a scan and are not asked do let us know. We may well be able to organise this.

If you have any questions please feel free to talk with any of the trial doctors or nurses.

Thank you for your participation in this trial
I agree to having a dual energy X-ray absorptiometry (DEXA) scan. I understand that this scan is purely for the purpose of the study in which I am participating and would not otherwise be part of my treatment. I understand this scan subjects me to a small radiation dose.

Name of Patient________________________ Date________________________ Signature________________________

Name of practitioner taking consent________________________ Date________________________ Signature________________________
13.8 General Practitioner information form

Trial using Thalidomide in the cachexia of incurable upper gastrointestinal adenocarcinomas

Information sheet for General Practitioners

Attach subject’s name and address here.

Dear Dr

The above patient has been entered into a randomised double blinded placebo controlled trial using Thalidomide in the cachexia of incurable upper gastrointestinal adenocarcinomas.

The trial is to determine whether Thalidomide is beneficial in preventing the cachexia often seen in incurable upper gastrointestinal adenocarcinomas and/or improving survival times. A small prospective placebo controlled study at the Queen Alexandra Hospital last year showed a reduction in weight loss in patients with terminal pancreatic cancers and a trend towards increased survival which did not reach statistical significance. The only two other published trials of Thalidomide in cancer cachexia showed good palliation of symptoms and reversal of weight loss.

Background:
The mechanism of the emaciation, weakness and malnutrition so frequently seen in patients with incurable gastrointestinal cancers is not completely understood. It cannot be explained solely by the reduced appetite and food intake of many cancer patients, nor can it be reversed with nutritional supplements or appetite stimulants alone. Recent work has suggested a role for many different cytokines and for catabolic products released from the tumour itself.

Thalidomide affects both mechanisms and has been shown to be helpful in the wasting associated with HIV and pulmonary TB. There are large trials currently in progress into its use for both haematological and solid organ malignancies. At present, few phase III trials have been conducted but preliminary data suggests a benefit in multiple myeloma, refractory Waldenström’s macroglobulinaemia, myelodysplasia, advanced prostate cancer, renal-cell carcinoma, high-grade glioma, melanoma and colorectal cancer, in some instances resulting in reduction of tumour bulk. Thalidomide’s
sedative and anti-emetic effects also allowed patients improved toleration chemotherapy in one trial.

**Trial:**
Subjects will be randomised to either placebo or Thalidomide 200mgs (four capsules) at night for six months. They will be followed up at weeks 0, 4, 8, 12 and 26. At each review they will be asked to complete a quality of life questionnaire and they will have basic measurements taken including height, weight, mid-arm circumference, triceps skin fold thickness and bioimpedance. They will be asked about potential side effects and have a clinical sensory assessment. Blood and urine samples will be taken at 0, 4, 12 and 26 weeks for full blood count, urea, electrolytes, liver function tests, markers of nutrition and inflammation and cytokine and tumour factor analysis.

All other medications they are on will continue as normal throughout the trial.

**Risks and side effects:**
The major risk of Thalidomide is its teratogenic effect in the first trimester of pregnancy. All subjects will be counselled regarding this prior to starting the trial. **Women of child-bearing potential or men whose partners are such must agree to either abstain from sexual intercourse or use two forms of effective contraception at the same time, one of which must be the male condom.** Women will need to have a negative pregnancy test prior to starting the trial and will have monthly tests throughout the trial.

Peripheral neuropathy is a recognised side effect of Thalidomide. Patients will therefore have a clinical sensory assessment at each visit. Any patient who develops peripheral neuropathy during the trial will be withdrawn.

Other side effects include:
Drowsiness, rash, constipation, and dizziness.

Patients will fill in a side effect questionnaire at each visit and have a contact number for the medical team involved should an adverse event occur. In previous trials Thalidomide has been well tolerated.

**Contact for further information:**
For further information you can contact Dr Susi Green (gastroenterology research registrar), Dr Patrick Goggin (gastroenterology consultant), or Mr Tim Johns (research nurse), at Queen Alexandra Hospital, Portsmouth. Contact No: 02392 286000 Extension 5470 Susannah.Green@porthosp.nhs.uk.
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