FINAL STUDY REPORT

Study Title:

The effects of eicosapentaenoic acid on biomarkers of growth and vascularity of human colorectal cancer liver metastases

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EUDRACT No. 2009-015903-22

R&D No. GA09/9094

MHRA No. 16767/0240/001-0001

Clincialtrials.gov No. NCT01070355

Chief Investigator: Prof Mark Hull

Sponsor: The University of Leeds

List of Principal Investigators and Sites	St James's University Hospital, Leeds, UK Spire Hospital Leeds, UK PI for both sites: Prof Mark Hull
List of Publications (or plans for publications) including those for patients (if applicable)	1. Oral presentation at the United European Gastroenterology Week, Amsterdam, Oct 2012. 2. Manuscript in preparation for publication.
Study Start and End Dates	Study start (1st patient recruited): 28/04/2010 Study end (last patient follow up): 12/10/2011
Study Design	A Phase II, randomised, double-blind, placebo-controlled trial of oral eicosapentaenoic acid 2g/day in patients awaiting resection of colorectal cancer liver metastases (CRCLM).
No. of Patients (planned and analysed)	Planned = 88 Recruited = 88 Analysed = 81 (43 placebo group + 38 EPA group) See attached CONSORT diagram
Main inclusion/exclusion criteria	**Study population:** Patients undergoing liver resection for treatment of CRCLM **Inclusion Criteria** (a) Age greater than or equal to 18 years (b) Either sex (c) Liver resection deemed clinically appropriate for management of metastatic CRCLM (d) Duration between decision to perform liver resection and surgery greater than 2 weeks (e) Ability to give written informed consent and follow study protocol (f) Telephone contact possible

	Exclusion Criteria (a) Neo-adjuvant chemotherapy for CRCLM (b) Chemotherapy for any cancer in the previous 3 months (c) Known bleeding diathesis or anticoagulation therapy (d) Fish or seafood allergy (e) Use of fish oil supplements (eg. cod liver oil) and unwilling to stop for the duration of the study (f) Pregnancy (g) Non-aspirin non-steroidal anti-inflammatory or corticosteroid use (h) Renal impairment (serum creatinine >150microg/l) (i) Active inflammatory disease (e.g. Inflammatory Bowel Disease, Rheumatoid Arthritis).
Investigational Medicinal Product(s) (including comparator, if applicable), mode of administration and batch number(s)	**IMP**: Eicosapentaenoic acid presented as a soft blue gelatin capsule containing 500mg of liquid highly purified eicosapentaenoic acid (>95%) in the free fatty acid form. Dose = 2g (4 capsules) daily. **Placebo**: capsules are identical in form to IMP, except for the replacement of EPA with the medium chain triglycerides capric and caprylic acid. Dose = 4 capsules daily.
Duration of Treatment	**EPA group**: median 30 days (range 12-65 days) **Placebo group:** median 26 days (range 15-73 days)
Primary and Secondary Objective(s)	1. To demonstrate the safety and tolerability of EPA in patients with CRCLM 2. To investigate the effect of EPA on biomarkers of CRCLM tumour growth and vascularity
Endpoints/ Outcome Measure(s)	**<u>Primary endpoint:</u>** **Ki67 tumour proliferation index** No difference between groups **<u>Secondary endpoints:</u>** **Safety and tolerability of EPA** EPA was safe and well tolerated. See attached summary of adverse events. There was an increase in gastrointestinal symptoms (diarrhoea, indigestion) in the EPA group whilst taking study medication. Two patients in the EPA group were withdrawn from the study because of diarrhoea All other adverse events were mild. There was no difference between groups in post-operative adverse events, need for blood transfusion, or length of hospital stay. Note that all post-operative adverse events were in keeping with the expected post-operative course for liver resection patients, that patients had stopped taking study medication the day before surgery, and that these adverse events were not attributed to study medication. **neo-CK18 tumour apoptosis index** No difference between groups

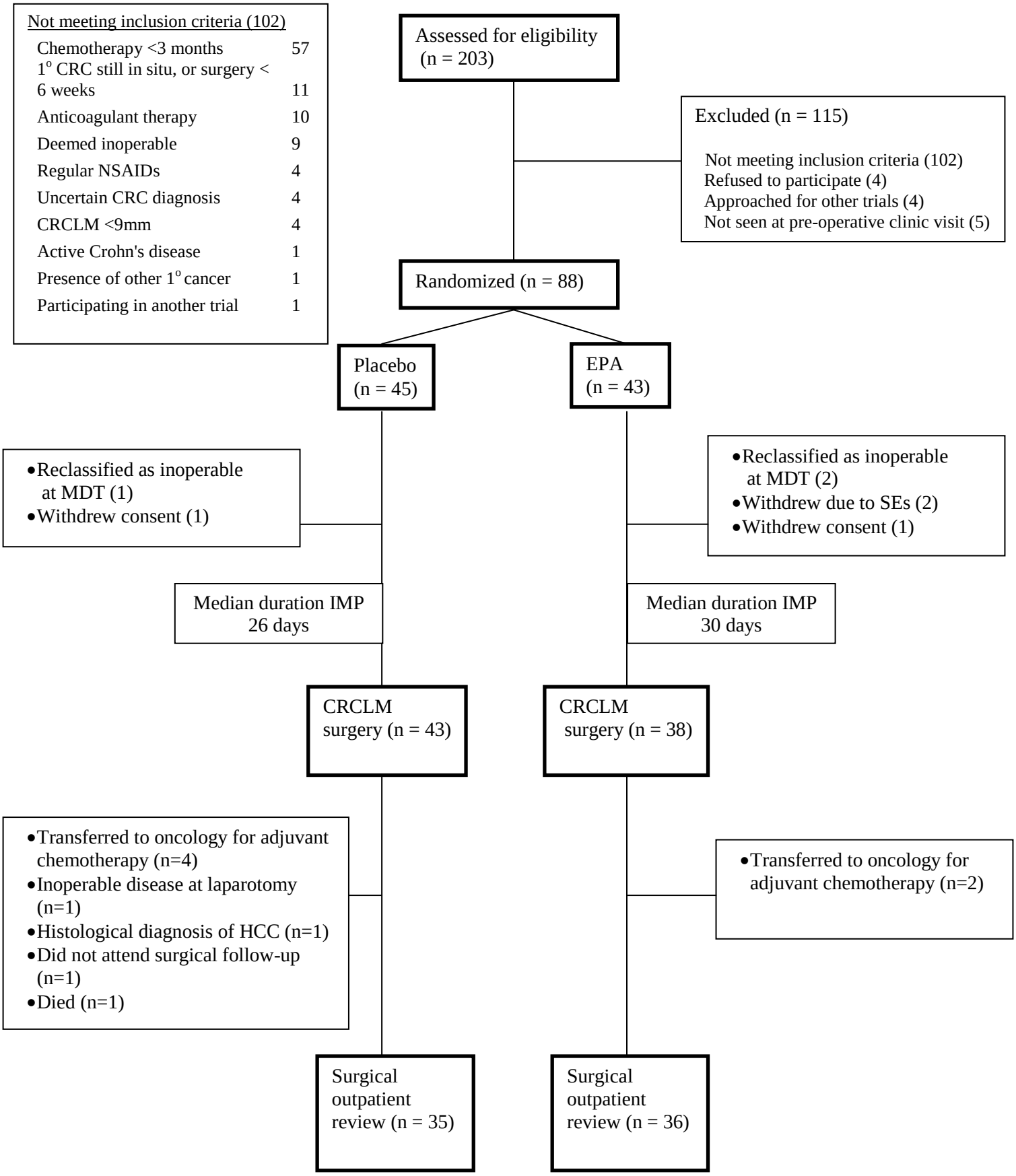
	CD31 tumour microvessel density There was a trend towards reduced tumour vascularity in the EPA group. **Tumour polyunsaturated fatty acid levels** There was a significant increase in tumoural EPA and reduction in arachidonic acid:EPA ratio in the EPA group. **Tumour PGE_2 levels** No difference between groups **Urinary PGE-M levels** PGE-M was significantly reduced post-treatment in the EPA group compared to placebo group. **Platelet aggregation** No difference between groups. Importantly there was no reduction in platelet aggregation in the EPA group, allaying concerns about an increased risk of bleeding with EPA supplementation. **Nuclear NFκB DNA binding in peripheral blood mononuclear cells** Nuclear NFκB DNA binding was significantly reduced in the EPA group post-treatment compared to baseline, and returned to baseline levels after cessation of treatment. No change in DNA binding was seen in the placebo group.
Statistical Methods	Parametric (such as Student's t test) and non-parametric tests (such as the Mann-Whitney U test) were used as appropriate to evaluate differences between EPA and placebo groups for all outcome measures.
Conclusions	EPA therapy is safe and well tolerated in patients with CRCLM EPA incorporates into CRCLM tissue EPA may reduce tumour vascularity EPA reduces systemic PGE_2 and inhibits PBMC NFκB DNA binding Further evaluation of EPA for CRCLM treatment/prevention is warranted

Authorised by: **Mr Andrew Cockbain**

Signature: 

Date: **03/11/2012**

The EMT Trial CONSORT diagram



The EMT Trial: Summary of baseline characteristics and adverse events

	Placebo n=45	EPA n=43	P=
Patient characteristics			
Age (years)	71 (35-87)	68 (44-82)	0.973
Sex M:F	35:10 (78%M)	26:17 (61%M)	0.078
Aspirin	10 (22%)	10 (23%)	0.908
Clopidogrel	3 (7%)	1 (2%)	0.328
Previous fish oil	9 (20%)	5 (12%)	0.283
Primary bowel cancer characteristics			
Dukes stage A B C D	 2 (4%) 13 (29%) 10 (22%) 20 (44%)	 2 (5%) 11 (26%) 17 (40%) 13 (30%)	0.331
Node Positive	25 (56%)	26 (61%)	0.641
Synchronous CRLM	20 (44%)	13 (30%)	0.169
Liver metastasis characteristics			
Interval between primary CRC surgery and presentation with CRLM (metachronous disease only)	19 months (3-80) n= 30	24 months (6-91) n= 32	0.161
Number of patients presenting for redo liver resection	11 (24%)	6 (14%)	0.213
Number of metastases	2 (1-5)	1 (1-9)	0.443
Largest metastasis (cm)	2.6 (0.9-12)	3.1 (0.9-15)	0.151
Previous chemotherapy			
Adjuvant chemotherapy > 3months prior to CRLM resection	20 (44%)	20 (47%)	0.846
Interval between end of chemotherapy and CRLM resection	12 months (5-73)	13 months (6-82)	0.885

- All data presented as n=(%) or median(range) unless stated.

Adverse events and withdrawals	Placebo n=45	EPA n=43	
Patients experiencing any adverse event	11 (24%)	15 (35%)	0.283
Total Adverse Events	**14**	**20**	
Preoperative adverse events			
• Diarrhoea	3 (7%)	8 (19%)	0.091
• Upper GI upset	0	5 (12%)	0.009
Postoperative adverse events			
• Encephalopathy (postoperative)	1	1	
• Postoperative collection	2	1	
• Bleeding	0	1	
• Wound infection requiring antibiotics	2	1	
• Wound infection no antibiotics	2	0	
• Lower respiratory tract infection	4	0	
• Urinary tract infection	0	3	
Withdrawals (all pre-operative)			
• Due to adverse events	0	2 (5%)	
• Reclassified as inoperable	1 (2%)	2(5%)	
• Consent withdrawn	1 (2%)	1 (2%)	
Surgical outcomes	**Placebo n=43**	**EPA =38**	**P=**
Extent of resection			0.752
• Minor	30 (70%)	25 (66%)	
• Major	9 (21%)	10 (26%)	
• Extended	3 (7%)	3 (8%)	
• Inoperable	1 (2%)	0 (0%)	
Packed red cell transfusion	4 (10%)	3 (8%)	0.822
HDU stay (days) *median + IQR*	1 (1-3)	2 (0-2.25)	0.954
Total hospital stay (days) *median + IQR*	7 (5-10)	6.5(5-9)	0.724

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- Extent of resection classified according to the IHPBA Brisbane 2000 classification as:
  Minor: 1-2 segments resected
  Major: 3-4 segments resected
  Extended: ≥ 5 segments resected