EMT2:
EPA for Metastasis Trial 2

A randomised placebo-controlled phase III trial of the effect of the omega-3 fatty acid eicosapentaenoic acid (EPA) on colorectal cancer recurrence and survival after surgery for resectable liver metastases

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(during office hours only)	

2. Contents

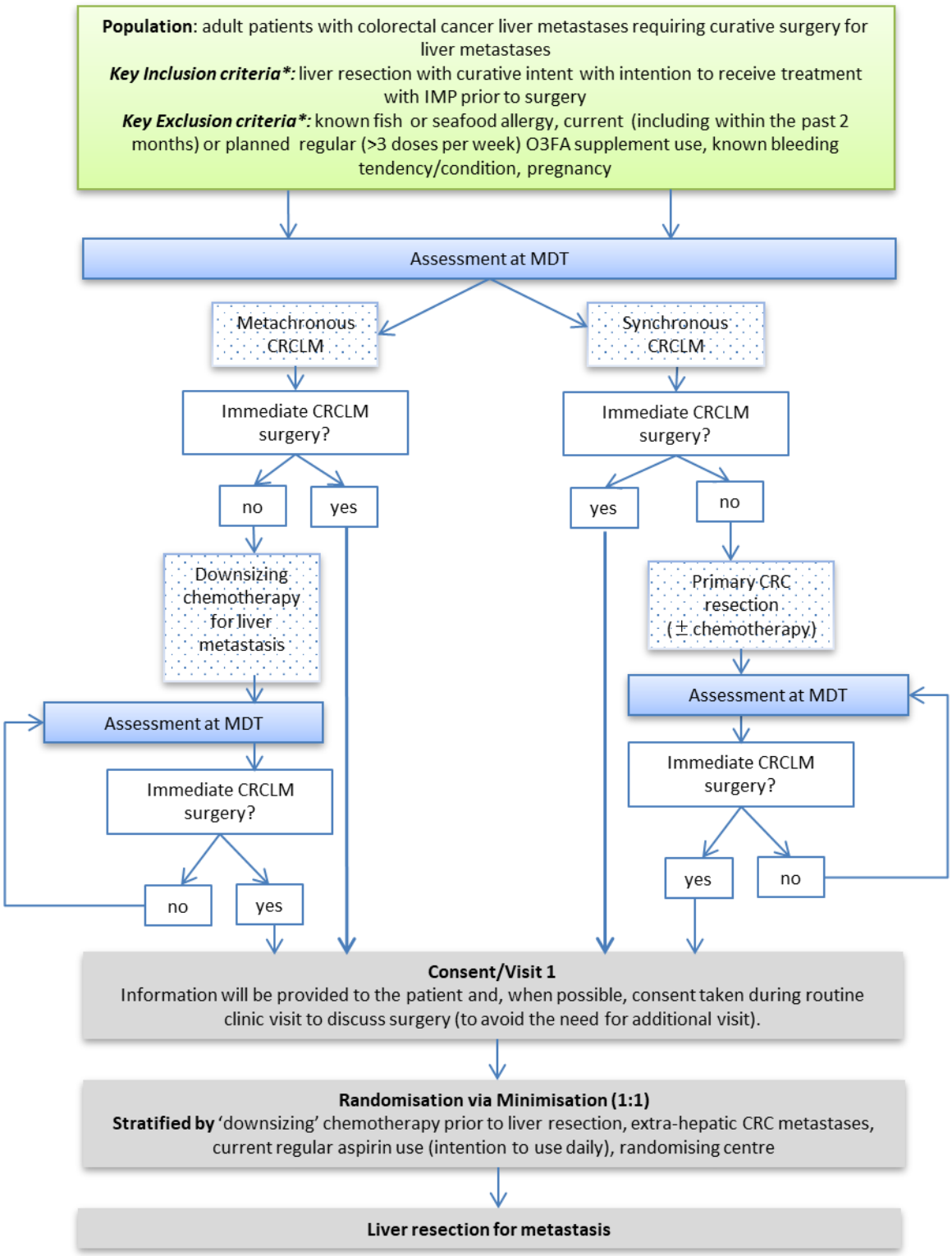
3. Trial Summary

Title	A randomised placebo-controlled phase III trial of the effect of the omega-3 fatty acid eicosapentaenoic acid (EPA) on colorectal cancer recurrence and survival after surgery for resectable liver metastases
Acronym	EMT2
Background	Despite significant advances in diagnosis and treatment of colorectal cancer (CRC), it remains the second most common cause of cancer-related death in the UK. The majority of deaths from CRC are related to distant metastasis, predominantly to the liver. Overall 5-year survival following liver resection and adjuvant chemotherapy for colorectal cancer liver metastases (CRCLM) is, at best, 40-60%. Despite surgery with curative intent, up to 60% of patients develop recurrence within 2 years of surgery. A randomised controlled trial (RCT) of the omega-3 fatty acid (O3FA) eicosapentaenoic acid (EPA) addressing anti-neoplastic activity demonstrated that treatment with EPA 2g daily for 6 months was associated with a significant reduction in rectal adenoma size and multiplicity compared with placebo. There is pre-clinical evidence that O3FAs reduce existing CRC tumour growth in rodent models of metastasis. The EMT study was a Phase II RCT of EPA 2 g daily in patients (n=88) undergoing liver resection surgery for CRCLM. Although there was no difference in the primary endpoint (tumour proliferation index), metastases from the EPA arm had a lower vascularity score (suggesting possible anti-angiogenic activity) than placebo-treated tumours. Although EPA (or placebo) treatment was limited to the pre-operative period, overall survival (OS) and disease-free survival (DFS) were specified as exploratory end-points on the basis that oral dosing with EPA before liver surgery would provide tissue EPA exposure in the immediate peri-operative period with prolonged bioavailability in the post-operative period due to the slow tissue 'washout' kinetics of EPA. Survival analysis demonstrated that the median DFS in the EPA group was 22.6 months compared with 14.7 months in the placebo group. Any DFS benefit was explained by a reduction in CRC recurrence from 12 months after surgery onwards.
Design	A randomised, double-blind, placebo-controlled, multi-centre, phase III trial of the omega-3 fatty acid (O3FA) eicosapentaenoic acid (EPA) as the ethyl ester (icosapent ethyl [IPE; Vascepa® or Vazkepa®]) in patients undergoing liver resection surgery for colorectal cancer liver metastasis (CRCLM) with curative intent.
Objectives	<u>Primary</u> • To determine whether icosapent ethyl (IPE) treatment improves Progression-Free Survival (PFS)

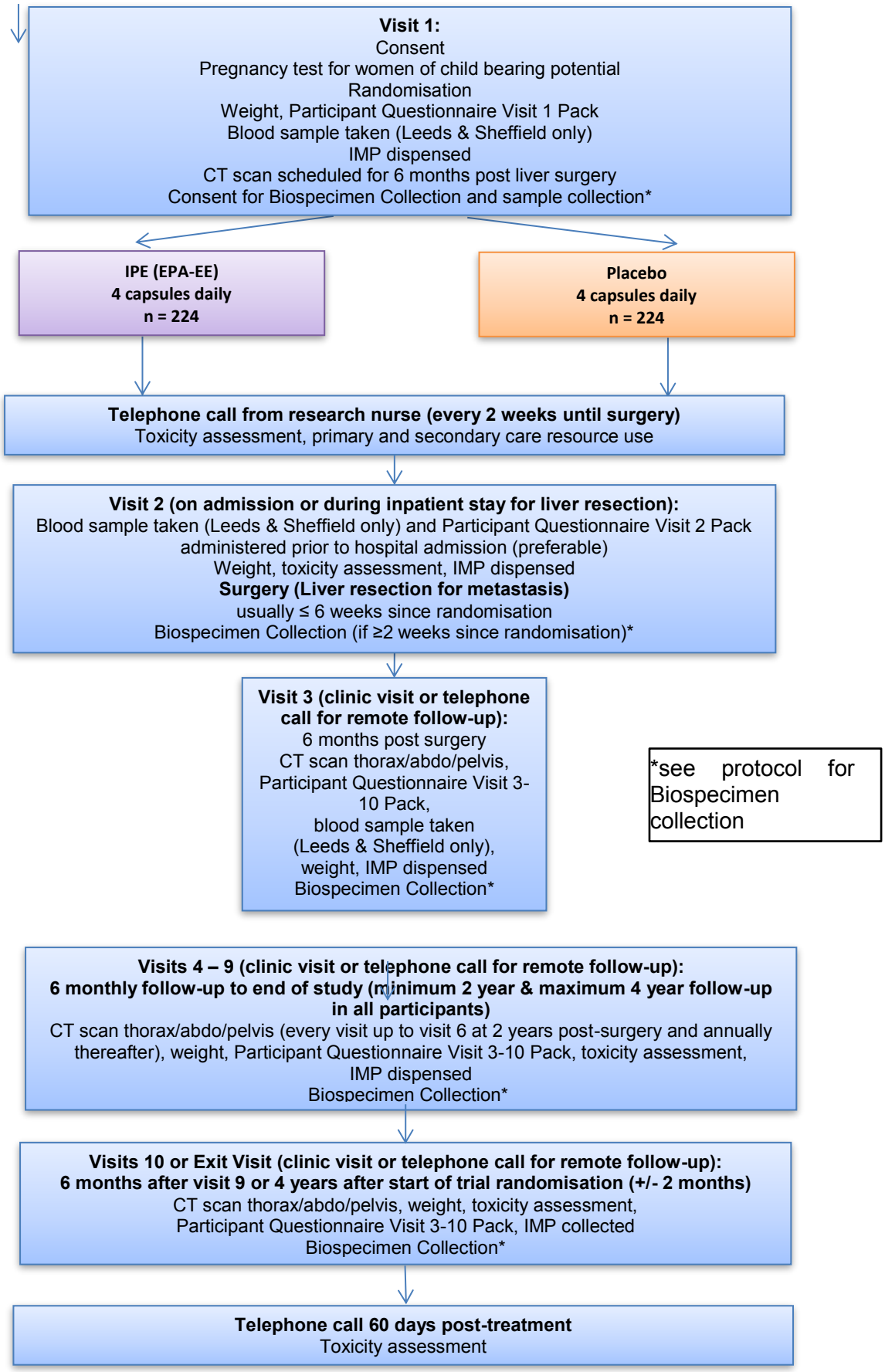
	<u>Secondary</u> • To determine whether IPE treatment improves overall survival (OS) (key secondary objective) • To confirm the safety and tolerability profile of IPE before and after surgery, including during cancer chemotherapy • To determine whether IPE treatment improves quality of life (QoL) after CRCLM surgery • To perform a health economic analysis of IPE treatment starting before and continuing after CRCLM surgery • To determine whether IPE treatment has an effect on the diagnosis of new primary cancers (excluding DCIS, cervical carcinoma *in situ*, superficial bladder carcinoma where treatment consisted of resection only and non-melanoma skin cancer where treatment consisted of resection or radiotherapy only) <u>Exploratory</u> • To determine whether baseline, pre-operative and/or 6 month post-operative red blood cell EPA content predicts disease-related outcomes • To determine whether IPE treatment maintains muscle mass in CRCLM patients and whether there is any association between changes in muscle mass and disease-related outcomes
Endpoints	Primary endpoint: • Progression Free Survival (PFS) during a minimum of 2 years follow up. Secondary endpoints: • Overall Survival (OS) • Safety and tolerability profile of IPE including during chemotherapy • Participant-reported quality of life after CRCLM surgery • Cost-effectiveness of IPE treatment • New primary cancers (excluding DCIS, cervical carcinoma in situ, superficial bladder carcinoma where treatment consisted of resection only and non-melanoma skin cancer where treatment consisted of resection or radiotherapy only) Exploratory endpoints: • Red blood cell EPA content • Muscle mass in CRCLM patients measured by abdominal CT scan
Population	Adult individuals listed for CRCLM resection with curative intent.
Randomisation	Randomisation (1:1) to receive either IPE capsules or placebo capsules.

Dose	4 capsules per day containing IPE (equivalent to 4 g EPA-ethyl ester [EE] daily) or 4 placebo capsules per day
Duration	Participants will start treatment before CRCLM surgery and will continue to receive treatment for a minimum of 2 years and a maximum of 4 years post-liver resection. Participants are followed up for 60 days beyond the end of treatment.
Evaluation of outcome measures	Participants are clinically assessed 6 months post-operatively (from liver resection) and at 6-monthly intervals thereafter for disease progression/recurrence. QoL outcomes are assessed using the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 supplementary module questionnaires. Health economic outcomes are assessed using a modified UK Cancer Costs Questionnaire Version 2.0 and data collected at each trial visit and telephone call. Adverse events will be documented during study treatment and follow-up. Measurement of the red blood cell fatty acid content will be performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) measurement of individual fatty acid (FA) species. Changes in lean body mass will be measured longitudinally from routine CT abdomen images based on muscle area at the L3 vertebral level.

4. Trial Schema



* Full inclusion and exclusion criteria in Section 9


Visit 1:
Consent
Pregnancy test for women of child bearing potential
Randomisation
Weight, Participant Questionnaire Visit 1 Pack
Blood sample taken (Leeds & Sheffield only)
IMP dispensed
CT scan scheduled for 6 months post liver surgery
Consent for Biospecimen Collection and sample collection*
IPE (EPA-EE)
4 capsules daily
n = 224
Placebo
4 capsules daily
n = 224
Telephone call from research nurse (every 2 weeks until surgery)
Toxicity assessment, primary and secondary care resource use
Visit 2 (on admission or during inpatient stay for liver resection):
Blood sample taken (Leeds & Sheffield only) and Participant Questionnaire Visit 2 Pack administered prior to hospital admission (preferable)
Weight, toxicity assessment, IMP dispensed
Surgery (Liver resection for metastasis)
usually ≤ 6 weeks since randomisation
Biospecimen Collection (if ≥2 weeks since randomisation)*
Visit 3 (clinic visit or telephone call for remote follow-up):
6 months post surgery
CT scan thorax/abdo/pelvis,
Participant Questionnaire Visit 3-10 Pack,
blood sample taken
(Leeds & Sheffield only),
weight, IMP dispensed
Biospecimen Collection*
*see protocol for Biospecimen collection
Visits 4 – 9 (clinic visit or telephone call for remote follow-up):
6 monthly follow-up to end of study (minimum 2 year & maximum 4 year follow-up in all participants)
CT scan thorax/abdo/pelvis (every visit up to visit 6 at 2 years post-surgery and annually thereafter), weight, Participant Questionnaire Visit 3-10 Pack, toxicity assessment,
IMP dispensed
Biospecimen Collection*
Visits 10 or Exit Visit (clinic visit or telephone call for remote follow-up):
6 months after visit 9 or 4 years after start of trial randomisation (+/- 2 months)
CT scan thorax/abdo/pelvis, weight, toxicity assessment,
Participant Questionnaire Visit 3-10 Pack, IMP collected
Biospecimen Collection*
Telephone call 60 days post-treatment
Toxicity assessment

5. Abbreviations and Glossary

Abbreviation	Definition
AA	Arachidonic acid
AE	Adverse Event
ALA	Alpha-linolenic acid
AR	Adverse Reaction
CI	Chief Investigator
COX	Cyclooxygenase enzymes
CRC	Colorectal cancer
CRCLM	Colorectal cancer liver metastasis
CRF	Case Report Form
CT	Computerised tomography
CTRU	Clinical Trials Research Unit
DCIS	Ductal carcinoma *in situ*
DHA	Docosahexaenoic acid
DFS	Disease-free survival
DMEC	Data Monitoring and Ethics Committee
DPA	Docosapentaenoic acid
EDTA	Ethylenediaminetetraacetic acid
EPA	Eicosapentaenoic acid
EPA-EE	Eicosapentaenoic acid ethyl ester
EPA-FFA	Eicosapentaenoic acid free fatty acid
EPA-TG	Eicosapentaenoic acid triglyceride
GCP	Good clinical practice
HR	Hazard ratio
IB	Investigator brochure
ICT	Institute of Cancer Therapeutics
IMP	Investigational medicinal product
IPE	Icosapent ethyl
ITT	Intention to treat
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MDT	Multi-disciplinary team

MHRA	Medicines and Healthcare products Regulatory Agency
NOAC	New oral anticoagulant
O3FA	Omega-3 fatty acid
O6FA	Omega-6 fatty acid
OS	Overall survival
PFS	Progression-free survival
PG	Prostaglandin
PI	Principal Investigator
PIS/ICF	Participant Information Sheet and Informed Consent Form
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RN	Research nurse
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TG	triglyceride
TMG	Trial Management Group
TSC	Trial Steering Committee

Term	**Definition**
Kit-code	Unique numerical identifier used to identify the IMP boxes without revealing the treatment allocation.
Replenishment	A repeat allocation of trial IMP via the CTRU 24-hr automated system.
Replacement	A repeat allocation of trial IMP via the 24-hr automated system which takes place at an unscheduled time point.
Safety Statistician	An independent CTRU statistician responsible for undertaking tasks that require knowledge of the treatment allocation.
Authorised Unblind Individual (AUI)	A member of CTRU staff who is permitted to have knowledge of treatment allocation but is not part of the trial team or the safety statistician. The individual is authorised to perform tasks and processes where knowledge of treatment allocation is required. This ensures the blind is not compromised for the blinded members of the team. A trial may have multiple people designated as AUI.

6. Background

6.1 Colorectal cancer and liver metastasis

Despite huge advances in diagnosis and treatment of colorectal cancer (CRC), it remains the second most common cause of cancer-related death with 15,903 deaths from CRC in the UK in 2014[1].

Despite significant improvements in survival from CRC, overall five-year survival for CRC is still only 59%[1]. The majority of deaths from CRC are related to distant metastasis (predominantly to the liver)[2]. Approximately half of all CRC patients will develop liver metastasis (CRCLM), median survival from which, without treatment, is only 6 months (increasing to >24 months with systemic chemotherapy)[2].

Liver metastases are surgically resectable in 10-20% of cases and this provides the only prospect of cure (20% long-term [>10 year] disease-free survival)[2-3]. Overall 5-year survival following liver resection and adjuvant chemotherapy for CRCLM is, at best, 40-60%[2]. The use of oxaliplatin-based chemotherapy (oxaliplatin/5-fluorouracil or oxaliplatin/capecitabine) has become integral to management of resectable CRCLM[2]. However, timing of chemotherapy for resectable disease remains controversial with some cases receiving neoadjuvant (pre-operative) chemotherapy rather than post-operative adjuvant chemotherapy[4]. Some patients with unresectable CRCLM also undergo a trial of chemotherapy aiming to 'downsize' their disease prior to a final decision regarding resectability[2,4]. Despite surgery with curative intent, up to 60% of patients develop recurrence within 2 years of surgery[3]. Approximately 20% of these are eligible for second or 're-do' hepatectomy, with similar post-operative outcomes to the first resection[5], but the remainder have incurable disease, which is invariably fatal.

6.2 Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (O3FAs) are naturally occurring lipids consisting of a variable length carbon chain with a methyl group at one (the omega [ω]) end and a carboxylic acid group at the other (alpha) end[6]. They contain more than one C-C double bond, one of which is located at the third C atom (ω3) from the omega end. The dominant long-chain (≥13 carbons) O3FAs in nature are C18:3ω3 (where X:Y denotes the carbon chain-length:number of C-C double bonds) alpha-linolenic acid (ALA), C20:5ω3 eicosapentaenoic acid (EPA) and C22:6ω3 docosahexaenoic acid (DHA)[6]. The majority of O3FAs reside naturally in a triglyceride (TG) form in the phospholipid bilayer of all cells. EPA and DHA have physiological (structural and signalling) activity as integral components of the cell plasma membrane in humans but ALA is believed to be inactive. ALA is found in significant quantities in seed oils, plants and vegetables. However, ALA is a poor substrate for human elongase and desaturase enzymes meaning that the dominant dietary source of EPA and DHA is restricted to cold-water oily fish such as salmon, mackerel and herring[7]. A 100 g portion of oily fish contains approximately 1 g O3FAs[8]. In contrast, omega-6 fatty acids (O6FAs) such as C18:2ω6 linoleic acid are ubiquitous in vegetable oils used widely in the 'western' diet, leading to a preponderance of C20:4ω6 arachidonic acid (AA) over O3FAs in human cell membranes[7-8].

O3FAs are widely available as nutritional supplements, either as a complex mixture of naturally-occurring variable chain-length O3FAs (predominantly EPA and DHA) in fish oil (250-300 mg/g) or more commonly as a soft-gelatin capsule formulation, in which EPA alone, or in combination with DHA, is concentrated (to >300 mg/g)[7]. O3FAs can be presented in the TG form, as the ethyl ester (EE), or as the free fatty acid (FFA)[9].

Pancreatic lipase stimulated by food (especially fat) intake hydrolyses O3FA-TGs producing O3FA FFAs, which are absorbed by small intestinal enterocytes before re-esterification to the TG form for chylomicron transport to the liver and eventual systemic distribution leading to incorporation into all plasma cell membranes[9]. Omega-3 fatty acid EEs require hydrolysis by carboxyl-ester lipase (also known as bile salt-dependent lipase) in order to generate FFAs for enterocyte uptake[9]. Presence of pancreatic lipase and carboxyl-ester lipase in the intestinal lumen is critically dependent on stimulation of pancreatic secretion by food intake. Food fat content has been demonstrated to affect O3FA tissue incorporation after short-term administration of EEs[10].

Systemic O3FA bioavailability is most accurately and reliably measured in clinical studies by quantification of red blood cell (RBC) O3FA levels[11]. Oral dosing studies have determined that O3FA tissue incorporation approaches steady-state levels at two weeks after starting supplements, reaching a peak between 4-6 weeks, and that 'washout' to basal levels can take as long as 3 months[12]. Recently, whole blood O3FA testing from dried finger-prick blood samples has emerged as an alternative to venepuncture needed for RBC isolation[13]. Preliminary data suggest a strong correlation between whole blood and RBC O3FA levels after O3FA supplementation[13].

There have been few direct comparisons of bioavailability of EPA given as the FFA, TG and EE. Most studies have been short-term (≤ 2 weeks) and measured plasma/serum TG levels, which are of uncertain relevance to tissue omega-3 fatty acid incorporation[9] In the studies of El Boustani *et al.*[14,20] and Lawson and Hughes[15,17, 16,19], plasma TG levels were higher after FFA administration than TG ingestion, when omega-3 PUFAs were given with a low-fat meal. Interestingly, in the longer study of Dyerberg *et al.*[17], plasma TG levels after TG administration were in slight excess of those after FFA ingestion.

One comparison of tissue (RBC) EPA incorporation after longer-term mixed omega-3 PUFA administration as the –TG, -EE or krill oil (4 weeks) reported no significant difference between formulations with equivalent EPA and DHA content[18ref]. In another long-term (6 months) comparison of mixed EPA/DHA administration in TG and EE forms in hyperlipidaemic subjects, TG treatment resulted in a significantly greater % RBC content of EPA than the EE group[19].

Overall, the available data suggest little difference between bioavailability of the EPA-TG, EPA-EE and EPA-FFA forms of EPA, when EPA alone or an omega-3 PUFA mix is given with food[9]. By contrast, bioavailability of the EE form of EPA is more variable and more dependent on simultaneous food intake in short-term studies[9]. However, differences in 'bioavailability' of different formulations of mixed omega-3 PUFAs during long-term (weeks-months) dosing are insignificant and other factors (eg. compliance, other host factors) are likely to be more important than the type of omega-3 PUFA used.

Compliance (in turn, affected by tolerability of any given O3FA formulation) is likely to play an important role in tissue O3FA exposure but has not been studied formally. It is likely that variable compliance contributes to the significant intra-patient (coefficient of variation [CV] ~5%) and inter-patient variability (CV~10%) in O3FA levels (measured by red blood cell membrane content) recognised during medium-term (weeks) supplementation[9,20-22].

Similar TG-lowering effects of mixed EPA/DHA preparations in humans have been consistently observed for O3FAs in the TG, EE and FFA form suggesting that the chemical form of EPA does not affect clinical effectiveness during long-term dosing [22-23]. Moreover, O3FAs, either EPA alone or as an EPA-DHA mix, have demonstrated similar efficacy as the TG, EE or FFA in several rodent CRC models (see 6.2.1)[6].

6.2.1 Evidence that EPA has anti-CRC activity

Evidence that O3FAs have anti-CRC activity has been summarised elsewhere[6]. In brief, a large body of human observational studies has not demonstrated a relationship between dietary O3FA intake and CRC risk, perhaps because of methodological limitations of dietary measurement and/or modest dietary O3FA intake in most study cohorts[6]. By contrast, a strong and consistent signal that O3FAs have anti-CRC activity has emerged from rodent models of colorectal carcinogenesis[6]. The majority of pre-clinical studies have tested O3FA mixtures including both EPA and DHA. The limited number of studies investigating the anti-CRC activity of either EPA or DHA alone has demonstrated equivalence[6]. Pre-clinical evidence that O3FAs have anti-CRC activity has led to a number of colorectal mucosal biomarker studies which reported that oral dosing with an EPA/DHA mixture or EPA alone (1-4g per day) was associated with reduced epithelial cell proliferation and increased apoptosis[6].

Clinical studies looking at the chemoprevention efficacy of O3FAs have to date been restricted to EPA with no studies of pure DHA preparations. Importantly, EPA is considered to be the 'universal donor' such that C20:5ω3 EPA can be metabolised to C22:6ω3 DHA in humans via C22:5ω3 docosapentaenoic acid (DPA), which is reflected by increased DHA tissue content following EPA supplementation[24]. The first Phase III RCT of EPA addressing anti-neoplastic

activity demonstrated that treatment with 99% EPA-FFA 2g daily for 6 months was associated with a significant reduction in rectal adenoma size (29.8%) and multiplicity (22.4%) compared with placebo[24]. This preliminary observation prompted an adenomatous polyp prevention trial of EPA (using both 99% FFA 2 g and 90% TG 2870 mg daily [also equivalent to 2 g FFA]) and aspirin 300 mg daily in 'high risk' individuals (n=709) undergoing colonoscopic surveillance in the English Bowel Cancer Screening Programme, results of which are expected in 2017[25].

There is also pre-clinical evidence that O3FAs reduce existing CRC tumour growth in rodent models of metastasis[6]. It has been demonstrated that dietary supplementation with EPA-FFA (producing similar tissue EPA incorporation to that seen in clinical studies[24]) abrogated mouse MC-26 CRC cell liver metastasis after intra-splenic injection in *Balb/c* mice[26]. These experimental observations prompted a Phase II RCT of EPA-FFA 2 g daily in patients (n=88) undergoing liver resection surgery for CRCLM (the **E**PA for **M**etastasis **T**rial [EMT] study)[27].

The primary end-point of the EMT study was the histological CRC cell proliferation index, but safety and tolerability were key secondary endpoints. Due to the 'window of opportunity' trial design, EPA-FFA or placebo treatment was restricted to the pre-operative period (median EPA treatment duration 30 days). As expected, EPA treatment was associated with higher intra-tumoral EPA levels[27]. Although there was no difference in the primary endpoint (tumour proliferative index), metastases from the EPA arm had a lower vascularity score, suggesting possible anti-angiogenic activity, than placebo-treated tumours[27]. Adverse events in patients with CRCLM awaiting surgery were limited to mild GI upset, with withdrawal because of symptoms occurring in only two cases[27]. Importantly, there was no excess intra-operative or post-operative bleeding risk associated with EPA treatment in keeping with a lack of any clinically significant effect of EPA on bleeding events[27].

Although EPA (or placebo) treatment was limited to the pre-operative period, overall survival (OS) and disease-free survival (DFS) were specified as exploratory end-points on the basis that oral dosing with EPA before liver surgery would provide tissue EPA exposure in the immediate peri-operative period with prolonged bioavailability in the post-operative period due to the slow tissue 'washout' kinetics of EPA[12]. Survival analysis demonstrated that the median DFS in the EPA-FFA group was 22.6 months compared with 14.7 months in the placebo group. Any DFS benefit was explained by a reduction in CRC recurrence from 12 months after surgery onwards[27]. A Cox multivariate analysis revealed that EPA treatment was associated with improved DFS (hazard ratio [HR] 0.35 [95% confidence interval 0.15-0.79]). EPA use also conferred OS benefit with 7 CRC-related deaths in 41 evaluable CRCLM patients who received EPA-FFA compared with 14 deaths in 42 placebo group patients (HR 0.40 [95% confidence interval 0.16-1.0])[27].

The two previous adequately powered RCTs of perioperative chemotherapy in patients undergoing CRCLM resection, including the most recent New EPOC trial, both used PFS as the primary endpoint[28-29-]. These trials are not directly comparable to the EMT study due to differences in the study populations related to trial exclusion criteria and historical differences

in hepatobiliary surgical practice[27]. However, the median PFS in these trials[28-29-] and smaller preceding studies[30] is slightly longer (approximately 21 months *versus* 15 months) than the median PFS in the placebo arm of the EMT study[27]. Two-year OS in the EMT study was 71.5% compared with 78-79% OS in the control arm of the two most recent trials [28-29], perhaps related to not having preoperative chemotherapy as an exclusion criterion, and wider inclusion criteria in the latter trials.

6.2.2 Mechanisms of the anti-neoplastic activity of O3FAs

The mechanistic basis of the anti-CRC activity of O3FAs has not been fully elucidated. Multiple mechanisms of action almost certainly contribute to the anti-neoplastic activity[31]. For example, EPA (but to a much lesser extent DHA) is a substrate for the cyclooxygenase (COX) enzymes, which drive colorectal carcinogenesis[6]. EPA effectively inhibits COX-1 but leads to synthesis of 3-series prostaglandins (PGs) by COX-2 at the expense of pro-tumorigenic 2-series PGs such as PGE_2[26,31-32]. Alternatively, EPA and DHA alter membrane fluidity, which may inhibit pro-tumorigenic signalling through cell surface receptors such as the epidermal growth factor receptor[31]. More recently, O3FAs have been characterised as ligands for specific fatty acid G protein-coupled receptors such as GPR120[31]. The lipophilic, membrane-bound nature of the O3FAs and the above putative mechanisms of action are compatible with extended 'washout' after cessation of therapy and suggest that prolonged anti-CRC activity is plausible even after limited short-term treatment.

6.2.3 Interaction of EPA with other CRC treatment modalities

There is preliminary evidence that concurrent O3FA therapy may improve the efficacy of platinum-based chemotherapy of lung cancer[36] and further evidence that O3FAs may protect against muscle loss and improve quality of life in cancer chemotherapy patients[37]. There has been no large, randomised study of the effect of O3FA supplementation on chemotherapy outcomes in CRC patients except for two uncontrolled case series that support improved tolerability and nutritional parameters during both FOLFOX and FOLFIRI regimens[38-39].

Acetyl-salicylic acid (aspirin) may also have anti-CRCLM activity[40]. Adjuvant aspirin therapy in patients who have undergone primary CRC surgery is currently being tested in the Add-aspirin trial[41]. Aspirin (like EPA) inhibits COX-1 (by irreversible acetylation) and alters enzymatic activity of COX-2, leading to reduced prostaglandin production[42]. Therefore, a valid hypothesis is that aspirin and EPA may have additive anti-CRC activity.

6.3 O3FAs and cancer cachexia

Although recent systematic reviews of a small number of studies in other cancers, particularly pancreas, have not demonstrated a clear signal, it has been hypothesised that O3FAs may abrogate cancer cachexia (the clinical syndrome of weight loss, muscle atrophy, loss of appetite, fatigue and weakness) perhaps by anti-inflammatory properties[43]. One explanation

for the different effect of EPA on OS and DFS observed during the first 18 months post-surgical follow-up in the EMT study is that EPA could reduce cancer-related cachexia. Therefore, a valid hypothesis is that EPA treatment abrogates the reduction in muscle mass (termed sarcopaenia) that is an integral feature of the cancer-related cachexia syndrome. This can be tested by measuring lean body mass longitudinally using routine CT abdomen images using the method of Baracos (based on muscle area at the L3 vertebral level), in parallel with assessment of patient-reported symptoms[44].

6.4 Safety and tolerability of EPA treatment

Vast experience of O3FAs in a cardiology setting and from the informal 'over-the-counter' nutritional supplement market has confirmed that long-term O3FA supplementation is safe, with a restricted set of mild side-effects generally pertaining to the gastrointestinal tract such as dyspepsia, eructation and diarrhoea (all ≤10%)[45]. Total daily doses of O3FAs up to 4g are considered safe[45]. In practice, no excess bleeding risk has been observed in large-scale randomised controlled trials (RCTs) of doses of mixed O3FAs and pure EPA up to 2 g daily, including the EMT trial in CRCLM patients[27], despite some *ex vivo* evidence for anti-platelet activity of O3FAs[46]. Previous studies of O3FA use in cardiology patients taking anti-platelet and anti-coagulant drugs have not demonstrated any excess of bleeding events[45,47]. The Summary of Product Characteristics (SmPC) for the mixed O3FA preparation, which is licensed in the UK (Omacor®), advises that it has been used in conjunction with warfarin without haemorrhagic complications but advises that the prothrombin time should be checked if there is co-prescription with warfarin. The FFA and TG formulations, which have been used in current and previous RCTs in patients with, and at risk of, CRC have not raised any safety concerns[24,27]. In particular, there was no excess of peri-operative bleeding events in the group that received EPA prior to liver surgery compared with placebo in the EMT trial[27].

6.5 The IMP in EMT2

Icosapent ethyl (IPE) or Vazkepa®, also known as AMR101 or Vascepa® in the USA, (Amarin Pharmaceuticals Inc.), is approved by the Medicines and Healthcare Products Regulatory Agency (MHRA), European Medicines Agency (EMA) and US Federal Drug Administration (FDA) for prevention of cardiovascular events in individuals with established cardiovascular disease, or diabetes and at least one other cardiovascular risk factor, who are already taking a statin and have elevated blood triglyceride levels. It is available as 1 g (998 mg) EPA-EE in soft gelatin capsules. Therefore, each capsule contains the equivalent of 914 mg EPA-FFA. Dosing is recommended with meals. Pharmacokinetic studies have demonstrated a dose-response relationship with the plasma and red blood cell EPA level attained (and changes in

other red blood cell O3FAs), with IPE 4 g/day providing a significant increase in plasma and red blood cell EPA level after 12 weeks therapy compared with 2 g/day[48]. Plasma EPA levels (expressed as the % total fatty acids) in patients with hypertriglyceridaemia after 12 weeks treatment with 2 g/day and 4 g/day were 1.9% and 3.4-3.6% respectively[48-49]. An 8 week study in healthy volunteers of EPA FFA 2 g daily (used in EMT[27] and seAFOod[25] trials) resulted in plasma EPA levels of 4.6%[50]. Treatment with EPA FFA 2 g daily for a shorter period (median 30 days) in the EMT trial (which may not have generated steady-state O3FA levels) was associated with a similar % increase in red blood cell EPA content (240%)[27] to that seen with IPE 2 g/day for 12 weeks (300%; cf. 500% with 4 g/day)[48]. In a Japanese trial of 1800 mg EPA-EE per day for 5 years, the % change from baseline of serum EPA (as the % of total fatty acids) was only 126%[51]. Therefore, the available evidence suggests that dosing with 4 g/day IPE will produce EPA bioavailability most similar to that obtained with EPA-FFA and EPA-TG in previous CRC trials[52] with the caveats that there has been no direct comparison between different EPA formulations in CRC patients and that differences in methodology for measurement and reporting of plasma, serum and red blood cell EPA content mean that direct comparisons should be carried out cautiously.

Short-term studies have demonstrated no difference in bioavailability between single and split (BD) IPE dosing at 2 g/day[53]. Therefore, the dose of IPE used in the EMT2 trial (4 g/day) is recommended as a twice daily 2 g (2 x 1g capsules) dose.

A large (n=8179) randomised trial of IPE 4 g/day for prevention of cardiovascular disease with median follow-up of 4.9 years (REDUCE-IT; NCT01492361) reported that overall rates of adverse events and serious adverse events in the IPE group were not significantly different from placebo users[54]. Atrial fibrillation or atrial flutter occurred in 5.8% of subjects receiving IPE in REDUCE-IT compared with 4.5% in subjects receiving placebo[54]. Atrial fibrillation or atrial flutter requiring hospitalisation for 24 hours or more occurred in 3% of subjects treated with IPE compared with 2% in subjects receiving placebo. Atrial fibrillation and atrial flutter were reported more frequently in subjects with a previous history of atrial fibrillation or atrial flutter receiving IPE than in those receiving placebo (12.5% vs 6.3%)[54]. Bleeding occurred in 11.8% of subjects receiving IPE in REDUCE-IT compared with 9.9% in subjects receiving placebo[54]. Serious bleeding events were reported more frequently in subjects receiving IPE than in those receiving placebo when administered in combination with concomitant antithrombotic medication (3.4% vs 2.6%), but occurred at the same rate (0.2%) in subjects not taking concomitant anticoagulant/antiplatelet medication[54]. The bleeding events most frequently observed with IPE in the REDUCE-IT trial were gastrointestinal bleeding (3.1%), contusion (2.5%), haematuria (1.9%), and epistaxis (1.5%).

EPA-EE has been licensed in Japan since the 1990's as Epadel (Mochida Pharmaceutical Co.), at a 1800 mg dose (capsule or sachet), and, more recently (2013), in an OTC form

(Epadel T). This product has been the subject of the large (n=18645) JELIS trial[55], in which GI adverse events were reported in 3.8% (placebo 1.7%).

6.6 Rationale for the trial

Despite optimal multidisciplinary team management of patients with CRCLM using liver resection surgery and systemic chemotherapy, metastatic CRC of the liver remains a significant cause of cancer-related death with long-term survival occurring in a small minority of patients and with overall 5 year survival being typically only 40-60%. Therefore, there remains a need for safe, well-tolerated treatment that will improve outcomes for patients with CRCLM.

The EMT study suggested that short-term pre-operative treatment with EPA might provide long-term OS and DFS benefit in patients undergoing liver resection surgery for CRCLM. EMT2 will determine definitively whether prolonged EPA treatment, starting before surgery and continuing afterwards, reduces cancer progression, and secondarily whether there is an OS benefit, in CRCLM patients. For the EMT2 trial, PFS will be used as the primary endpoint on the basis that 1) participants will have clinically evident metastatic CRC at randomisation prior to liver surgery and 2) other major RCTs of outcomes after CRCLM surgery have employed PFS as the primary outcome measure. In addition, OS will be the key secondary outcome measure in order to explore any effect on OS after CRC progression during the intervention period (see Section 7.3).

7. Aims and Objectives

EMT2 is a randomised placebo-controlled, double-blind trial of EPA-EE (IPE) for CRCLM patients.

7.1 Aims

The trial aims to determine whether oral IPE therapy started before CRCLM surgery and continued for a minimum of 2 years post liver resection lengthens progression-free survival (PFS) in patients undergoing liver resection surgery for CRCLM with curative intent.

7.2 Primary Objective

- To determine whether IPE treatment improves progression-free survival (PFS) in CRCLM patients.

7.3 Secondary Objectives

- To determine whether IPE treatment improves overall survival (OS).
- To confirm the safety and tolerability profile of IPE before and after surgery, including during chemotherapy.
- To determine whether IPE treatment improves participant reported quality of life after CRCLM surgery.
- To perform a health economic analysis of IPE treatment.
- To determine whether IPE treatment has an effect on the diagnosis of new primary cancers (excluding DCIS, cervical carcinoma *in situ*, superficial bladder carcinoma where treatment consisted of resection only and non-melanoma skin cancer where treatment consisted of resection or radiotherapy only).

7.4 Exploratory Objectives

- To determine whether baseline, pre-operative and/or 6 month post-operative red blood cell EPA content predicts disease-related outcomes.
- To determine whether IPE treatment maintains muscle mass in CRCLM patients and whether there is any association between changes in muscle mass and disease related outcomes.

8. Design

The EMT2 study is a prospective randomised, double-blind, placebo-controlled, multi-centre, parallel-group, superiority phase III trial of the omega-3 fatty acid (O3FA) eicosapentaenoic acid (EPA) in patients undergoing liver resection surgery with curative intent for colorectal cancer liver metastases (CRCLM).

448 eligible participants will be randomised on an equal basis to receive 4 x 1 g capsules per day of either icosapent ethyl (IPE; equivalent to 4 g of EPA-EE or 3656 mg EPA-FFA) taken as 2 capsules twice daily with food or 4 placebo (containing light mineral oil instead of IPE) capsules taken in an identical fashion.

The trial is designed to investigate whether EPA (IPE) treatment will result in an improvement in PFS (see section 17.1.1 for definition).

EMT2 is a double-blind trial design in which participants and site personnel will be blinded to the treatment allocation to minimise the possible introduction of bias.

All participants will be followed up for a minimum of 2 years and a maximum of 4 years post liver resection (Please refer to Section 13 on Assessments/samples/data collection for more details on the follow-up schedule).

There is also the option for EMT2 participants to join a sub-study funded by The US National Institutes of Health called Prebiotic effect of eicosapentaenoic acid treatment for colorectal cancer liver metastases, in which biospecimens (stool, urine, blood, and tumour tissue) will be collected before and after EPA or placebo treatment (refer to the Biospecimen Collection protocol).

9. Eligibility

Eligibility waivers to inclusion and exclusion criteria are not permitted.

9.1 Inclusion criteria

- Aged ≥18 years
- Able to provide written informed consent
- Histological diagnosis of CRC with evidence of liver metastases
- Planned liver resection surgery for CRCLM with curative intent, including repeat 're-do' CRCLM liver surgery (a second independent resection for a separate CRC liver recurrence)
- Intention to receive IMP treatment prior to CRCLM surgery

9.2 Exclusion criteria

- Previous CRCLM surgery for the management of the **current** metastatic disease[1]
- Incurable extra-hepatic metastases
- Current (in the last 2 months) or planned regular (>3 doses per week) use of O3FA-containing drugs or supplements, including Vazkepa®, Omacor®, fish oil and cod-liver oil supplements
- Fish/seafood allergy
- Diagnosis of hereditary fructose intolerance

[1] Patients who have previously undergone CRCLM surgery and who present with new CRC liver disease in planned two-staged surgery are ineligible.

- Soya or peanut allergy
- Inability to comply with trial treatment and follow-up schedule
- Known bleeding tendency/condition (e.g. von Willebrand disease)
- A previous malignancy within the last 5 years other than:
  - colorectal cancer
  - non-melanoma skin cancer where treatment consisted of resection only or radiotherapy
  - ductal carcinoma *in situ* (DCIS) where treatment consisted of resection only
  - cervical carcinoma *in situ* where treatment consisted of resection only
  - superficial bladder carcinoma where treatment consisted of resection only
- A previous malignancy where the patient has been disease-free for ≤5 years
- Pregnant or breastfeeding women or women of childbearing potential not willing to use effective contraceptive measures[2]. Women of childbearing potential are defined as fertile, following menarche and until becoming post-menopausal, unless permanently sterile.
- Men defined as fertile (post-pubescent and not permanently sterile by vasectomy or bilateral orchidectomy) and not willing to use effective contraceptive measures[3] if appropriate.

9.3 Resection of primary colorectal cancer

It is expected that some patients may present with primary colorectal cancer and liver metastases concurrently. These patients are eligible for trial participation providing that both the primary colorectal cancer and the liver metastases are considered able to be resected curatively. Eligibility of participants should be confirmed at the point at which liver resection is definitely scheduled regardless of the primary CRC management.

9.4 Chemotherapy prior to liver resection

It is expected that some patients may require chemotherapy prior to liver resection surgery. Depending on the patient presentation, this may include chemotherapy for treatment of the

[2] Acceptable contraception is defined as one of the following: combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progesterone only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, practicing true abstinence (when this is in line with the preferred and usual lifestyle of the participant)

[3] Acceptable contraception is defined as: condom, consider contraception for non-pregnant partner during treatment until the end of systemic exposure in the male participant plus a 90 day period

primary colorectal cancer prior to resection of the liver metastases (for patients with a synchronous presentation) or 'downsizing' chemotherapy for liver metastases that are borderline operable.

Please note that it is necessary to determine the purpose of chemotherapy treatment prior to liver resection as 'downsizing' chemotherapy for borderline operable liver metastases is a stratification factor and must be confirmed prior to randomisation. Prior chemotherapy at any time-point is not an exclusion criterion for EMT2. However, patients must have completed chemotherapy and have an MDT recommendation for CRCLM resection with curative intent in order to be eligible for EMT2 participation.

Details of the chemotherapy treatment regimens will be recorded.

9.5 Prior and concurrent participation in other clinical trials

The eligibility of participants who have participated in other previous or concurrent trials will be determined on a case by case basis and must be discussed with the CTRU, Sponsor and the respective trial team prior to randomisation.

Co-enrolment with participants in the colorectal cohort of the Add-Aspirin trial (EudraCT 2013-004 398-28, Sponsor University College London) will be permitted providing that the respective eligibility criteria of each trial are fulfilled[41]. Add-Aspirin aims to assess whether regular aspirin use after standard therapy prevents recurrence and prolongs survival in participants with non-metastatic common solid tumours including CRC[41]. Add-Aspirin participants with CRC who go on to develop CRCLM may be eligible for EMT2 if liver resection with curative intent is considered appropriate. EMT2 participants are also permitted to participate in the Add-Aspirin study following CRCLM surgery if the participant fulfils the eligibility criteria defined by the current Add-Aspirin protocol; information on Add-Aspirin trial participation should be provided on the EMT2 Follow-Up CRF. This pragmatic trial design facilitates the assessment of the efficacy of EPA in participants who use aspirin which may become standard practice in the future. This approach also minimises any potential negative effects on recruitment due to competing trials in the same patient population.

9.6 Biospecimen collection to investigate the prebiotic effect of EPA treatment for CRCLM

Once an individual has provided written informed consent to participate in EMT2, the participant may be given the opportunity to take part in a sub-study, which involves collection of stool, urine, blood and tumour tissue during the EMT2 trial (See Biospecimen Collection protocol).

10. Recruitment Process

10.1 Recruitment Setting

Participants will be recruited from multiple research sites in England. Research sites will be required to have obtained management approval and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

The recruitment target requires that 448 participants are recruited over a 2 year period.

10.2 Eligibility Screening

Participating research sites will be required to complete a paper Screening Form for all those patients presenting to the hepatobiliary multi-disciplinary team (MDT) for consideration for liver resection surgery for CRCLM.

Documented reasons for ineligibility or patient declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Screening forms should be returned to CTRU on a monthly basis. Anonymised information will be collected including:

- Age
- Gender
- Date screened
- 'Downsizing chemotherapy (yes or no)
- Known extra hepatic CRC metastases with curative treatment planned (yes or no)
- Current regular aspirin use (yes to current use, no current use or Add-aspirin trial participant still receiving IMP)
- Reason not eligible for trial participation or
- Eligible but declined and reason for this or
- Other reason for non-randomisation

10.3 Informed Consent and Eligibility

The Principal Investigator (PI) will retain overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the current ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996. Informed consent must be obtained by a clinician authorised by the PI on a delegation log prior to the participant undergoing procedures that are specifically for the purposes of the study and are not standard routine care at the participating site.

Assenting participants will be broadly assessed for eligibility during the screening process based on their medical history according to the inclusion and exclusion criteria.

The right of a patient to refuse participation without giving reasons will be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

10.3.1 Initial Information and Initial Approach

Potential participants will be identified through the hepatobiliary MDT at the time of the decision to offer CRCLM surgery to that individual. Potential participants who require a primary CRC resection or 'downsizing' chemotherapy for liver metastases prior to CRCLM surgery should be reviewed for CRCLM surgery by the MDT again following primary CRC surgery/ 'downsizing' chemotherapy of CRCLM and assessed regarding eligibility for trial participation at that point.

Potential participants will be approached about the trial at the outpatient appointment, at which CRCLM surgery is discussed and will be provided with the full Participant Information Sheet and Informed Consent Form (PIS/ICF) at this time.

10.3.2 Consent Process

Potential participants will be given sufficient time (e.g. 1-2 hours or as considered sufficient by the individual) to independently consider the verbal and written trial information provided. Potential participants may be invited to provide their informed consent for the study at the time of the initial approach. This approach may be beneficial when patients have travelled a significant distance for tertiary-level clinical management and may not accept a dedicated research visit soon after the outpatient clinic appointment. A member of the site trial team may contact a potential participant by telephone and send the PIS/ICF in advance of the outpatient clinic visit in order to introduce the concept of the EMT2 Trial and research in general, particularly if there is likely to be a short period of time between the clinic assessment and likely CRCLM surgery.

However, if any potential participant requires more time to consider trial participation, this will be accommodated through an additional visit for consent and randomisation, with provision to take the PIS/ICF home for subsequent telephone contact by a research nurse. If the potential participant is interested in taking part in the study, the research nurse will arrange a dedicated clinic visit for the purpose of consent, randomisation and dispensing of treatment.

Assenting potential participants will be invited to provide written informed consent. The PI or any other clinician who has received Good Clinical Practice (GCP) training and is authorised

on the trial delegation log is permitted to take informed consent for trial participation. The right of the participant to refuse consent without giving reasons will be respected. Further, the participant will be told that they are free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be kept in the participants' medical notes. The original consent form(s) will be filed in the Investigator Site File, a copy of the consent form(s) will be given to the participant and a copy of the consent form(s) will be returned to the Clinical Trials Research Unit (CTRU), at the University of Leeds and another copy will be filed in the hospital notes (as per local practice).

After informed consent has been obtained for the EMT2 trial, the participant will be given the opportunity to decide whether to join the Biospecimen Collection sub-study by reading the separate PIS for this study. Informed consent and inclusion in the sub-study is independent of EMT2 participation (refer to study specific documentation).

10.3.3 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose mental capacity after informed consent has been obtained will continue trial treatment if considered appropriate by the PI and the participant's carer/family with the participant's best interests foremost in the decision making process. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

10.3.4 Eligibility Process

The MDT will assess eligibility for CRCLM liver resection using a recent CT scan to confirm that the CRCLM are resectable with curative intent. A trial clinician listed on the EMT2 Authorised Personnel Log will confirm suitability for surgery and eligibility for EMT2 but in the majority of cases, patients suitable for surgery are eligible for participation in the study.

Women of childbearing potential will have a pregnancy test following consent and prior to randomisation. Women found to be pregnant will not be randomised into the trial but will be registered and assigned a trial number for monitoring purposes.

A CT scan of the thorax/abdomen/pelvis will be used to confirm that the participant is eligible for curative CRCLM resection and may be collected retrospectively as part of the sarcopaenia analysis (see Section 13.14).

All EMT2 participants are eligible for the Biospecimen Collection sub-study if the NHS research site is taking part in the Biospecimen Collection sub-study.

10.4 Registration and Randomisation

10.4.1 Timing of Registration and Randomisation

Recruitment of some participants into the EMT2 trial requires a trial-specific investigation to confirm eligibility. Women of childbearing potential will require a pregnancy test prior to randomisation. Therefore, recruitment is a two-step process with all participants providing written informed consent for entry into the trial before the CTRU 24-hour registration/randomisation system is accessed.

Those participants who are not women of childbearing potential will be registered and randomised into the trial during the same telephone call/web session.

Those participants who are women of childbearing potential will be registered into the trial and will require a pregnancy test. Those participants who are confirmed not to be pregnant can then be randomised into the trial. Those participants who are confirmed to be pregnant must be registered into the trial but will not be randomised.

Informed written consent for entry into the trial must be obtained prior to registration. Following confirmation of written informed consent and eligibility, participants will be registered and randomised into the trial by an authorised member of staff at the trial site. All participants who consent to the trial must be registered. Where possible, the date for surgery should be booked prior to randomisation. Randomisation should take place as soon as possible after consent is obtained and eligibility confirmed, and will be prior to the day of CRCLM surgery.

10.4.2 Treatment Allocation

Participants will be randomised on a 1:1 basis to receive either IPE 4 g daily or placebo and will be allocated a trial number and a unique kit-code to identify which box of capsules (active [IPE]or placebo) will be dispensed. The participant's randomisation allocation will not be disclosed in order to maintain the blinding of the trial.

A computer-generated minimisation programme that incorporates a random element will be used to ensure that treatment groups are well balanced for the following participant characteristics, details of which will be required for randomisation:

- 'Downsizing' chemotherapy prior to liver resection* (yes or no)
- Known extrahepatic CRC metastases with curative treatment planned (yes or no)
- Current regular (intention to use daily) aspirin use:

  - yes to current regular aspirin use
  - no to current regular aspirin use
  - Add-aspirin trial participant still taking IMP (placebo or aspirin, double-blind trial so treatment allocation not required to be known at EMT2 randomisation)
- Randomising Centre
- Time between randomisation date and date of planned liver resection surgery (<2 weeks or ≥2 weeks)

*For definition see Section 9.4

10.4.3 Registration and Randomisation Process

Registration and randomisation will be performed centrally using the CTRU automated 24-hour telephone/web randomisation service. Authorisation codes and PINs, provided by the CTRU, will be required to access the randomisation system. Only authorised members of staff at the trial sites will be able to access the randomisation system.

Participants will be registered into the trial and issued a trial number. Women of childbearing potential will be required to take a pregnancy test prior to randomisation. Participants who are not women of childbearing potential may proceed directly to randomisation during the same telephone call/web session.

The following information will be required in order for the participant to be registered and randomised. The person performing the registration/randomisation should have all details to hand:

- Name and code (assigned by the CTRU) of trial site
- Name of person performing the registration/randomisation
- Patient initials, and date of birth
- Confirmation of eligibility
- Confirmation of whether the participant is a woman of childbearing potential
- Confirmation of written informed consent
- Stratification factors (see section 10.4.2)
- Planned operation date

Direct line for 24-hour registration/randomisation
0113 343 2290
Website for registration/randomisation:
https://lictr.leeds.ac.uk/webrand/

Please ensure that the Eligibility Checklist and Randomisation CRFs have been completed before starting the registration/randomisation process

At the end of the registration process a unique EMT2 trial participant identifier will be assigned. At the end of the randomisation process a unique kit-code will be provided which identifies the box of capsules that needs to be dispensed by pharmacy. The participant's randomisation allocation will not be disclosed in order to maintain the blinding of the trial.

10.4.4 Post Randomisation Actions

Two *Confirmation of Randomisation* notifications, detailing the participant details and the kit-code they have been allocated, will be sent to site by email: one to the nominated contact in the local research team and another to pharmacy. These notifications are generated and sent automatically from the CTRU. In the event of a system failure, the kit-code may need to be provided to the pharmacy directly by the member of site staff randomising the participant (this information will be provided as part of the randomisation procedure). Confirmation of randomisation will also be automatically sent to the local PI.

10.4.4.1 Pharmacy

The kit-code provided will inform pharmacy which box of capsules needs to be dispensed to the participant. Upon receipt of the *Confirmation of Randomisation/Replenishment/Replacement* notification the pharmacy will dispense the box with the required kit-code and will subsequently confirm to CTRU the kit-code of the box dispensed by peeling off the relevant section of the label containing the kit-code confirmation, attaching this to the *Confirmation of Randomisation/Replenishment/Replacement* received and returning this back to CTRU immediately by fax or by sending a scanned copy via secure email. The participant's trial number and initials should be recorded on the IMP box and on the corresponding codebreak envelope. The codebreak envelopes will be held securely by pharmacy in order to be available for any necessary emergency unblindings (see Section 12.3.1).

10.4.4.2 Research Team

At the end of the randomisation procedure, the trial participant identifier and kit-code must be added to the Randomisation CRF and all participant details must be added to the main

Participant ID Log. Once received by the research team, the *Confirmation of Randomisation* is filed in the EMT2 Investigator Site File.

11. Trial Medicinal Product Management

Please refer to the EMT2 Pharmacy and Investigational Medicinal Product (IMP) Study Site Operating Procedure (SSOP) for full details of the trial IMP management requirements.

Within the trial the following are classed as IMPs:

Eicosapentaenoic acid ethyl ester (EPA-EE [IPE])

- Composition: soft, amber to light yellow, oblong gelatin capsules, one capsule contains 1g (998 mg) pure EPA-EE equivalent to 914 mg EPA-FFA
- Supplied by Amarin Pharma Inc.

Placebo

- Composition: soft, amber to light yellow, oblong gelatin capsules containing light mineral oil
- Supplied by Amarin Pharma Inc.

For handling guidance of both EPA-EE (IPE) and placebo, please refer to the Investigator Brochure (IB).

In order to maintain the blinding of the trial, both the IPE and placebo capsules look identical and are identically packaged and labelled in bottles with the same study-specific label in accordance with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended). IMP boxes will be identified only by a unique kit-code assigned at random.

11.1 Supply and distribution

Stockport Pharmaceuticals at Stockport NHS Foundation Trust will act as the trial's Central Pharmacy and holds a Manufacturer's Authorisation for Investigational Medicinal Products (IMP).

The trial IPE capsules and placebo capsules are obtained from Amarin Pharma Inc. (Bedminster, New Jersey, USA). The capsule coating contains gelatin of animal origin and therefore is not suitable for vegetarians. IMP will be imported from the USA by Fisher Clinical Services (Horsham, UK) and will then be sent to the Central Pharmacy where the bottles and boxes will be labelled and packaged for trial purposes.

Labelled trial IMP boxes will be stored by Stockport Pharmaceuticals and distributed to participating centres on request by CTRU. CTRU will manage a record of IMP at participating centres and order replacement stock as required.

Management of IMP supply will be carried out by CTRU using a kit logistics application which is linked to the 24-hour randomisation system. The kit logistics application will allocate kit-code labelled IMP boxes, as assigned by the safety statistician, at randomisation and at each trial visit. An authorised member of the trial team will use the 24-hour telephone/web randomisation system to obtain a kit code for the IMP to be dispensed to a participant at each visit as required; this is known as replenishment. Should a participant require a dispensing before a scheduled replenishment visit or delivery (for example if they lose the capsules) an authorised member of the trial team will access the 24-hour telephone/web randomisation system to obtain a kit code to be dispensed. This is known as replacement.

Blinded management of the kit logistics application will be conducted by the Senior Trial Co-ordinator. Management of the kit-code lists uploaded to the kit logistics application will be conducted unblinded by the CTRU Safety Statistician. In addition to the automated system, there will be a back-up kit-code list for each site which will also be maintained by the CTRU Safety Statistician. The CTRU Safety Statistician will be responsible for maintaining all kit-code lists and all lists will be securely password-protected when treatment information is contained within the list.

Trial IMPs (IPE and placebo) will be provided to sites free of charge for use in this clinical trial.

11.2 Prescribing and participant supply management

Each box contains seven bottles of IMP capsules (130 capsules in each bottle) and is sufficient for approximately 7 months of trial treatment (to allow for a standard 6 month treatment period and incorporating a +/- 2 week window around the visit date). One box of IMP capsules will be dispensed to participants at the start of treatment (visit 1) and at visit 3/trial telephone call onwards. It is expected that the entire box of IMP capsules dispensed at visit 1 will not have been used by visit 2. However, a repeat dispensing of IMP should be dispensed at visit 2 if surgery is >2 weeks after randomisation to cover a possible trial treatment period in excess of 7 months between visit 1 and visit 3.

Participants will be asked to bring in their IMP boxes at each trial visit or report the number of capsules remaining at a trial telephone call so that the participant's IMP can be checked by the research nurse with regards to the amount of IMP remaining and the expiry date. If the participant requires a further supply of IMP to ensure that there is sufficient IMP to continue treatment until the next trial visit (i.e. a 7 month supply), an additional box will be dispensed. The participant will be informed that all capsules from the first box must be used before the second box is opened and used and will be reminded regarding the expiry date of the IMP, if necessary.

The expiry date of the capsules will be printed on the bottle and box labels, the IMP bottles and the IMP box and the participant will be responsible for checking on an ongoing basis that the capsules being used have not expired. The participant will be provided with a Participant Drug Tracking Card which will list the visit/telephone call numbers, visit date/telephone call dates, kit-codes and expiry dates of all IMP boxes dispensed to the participant to aid in tracking which IMP box to use. Participants will be asked to return any expired IMP supply to clinic when attending trial visits. For participants undertaking telephone clinic follow-up due to distance from the trial site hospital, participants will be asked to store all unused/expired IMP until it is collected at the end of the trial.

Since IMP will be dispensed at each visit, it is expected that the participant may eventually accumulate sufficient IMP to last until the next trial visit and a dispensing will not be required. It is the responsibility of the prescribing healthcare professional to determine whether the participant has sufficient IMP with an appropriate expiry date (i.e. a 7 month supply) to miss a dispensing episode.

11.3 Dispensing

The relevant site pharmacist will be notified by the CTRU of all randomisations, replenishments and replacements at that site, either by fax or secure email; each *Confirmation of Randomisation/Replenishment/Replacement* notification will detail the participant trial ID number, date of birth, initials and the kit-code assigned to that participant. In order to maintain the blinding of the trial the pharmacist will not be informed of the participant's treatment allocation.

Each box of trial IMP, identifiable only by the unique kit-code, will have a corresponding code-break envelope. Each time a box is dispensed, the participant identifiers must be added to the trial IMP box label and also to the corresponding code-break envelope by the dispensing pharmacist. This code-break envelope will then be held securely within the site pharmacy for access required in the event of unblinding (see Section 12.3.1).

At each dispensing the participant will receive one trial IMP box, containing seven bottles (130 capsules per bottle, providing 910 capsules per box), of either IPE or placebo.

Participants will take 4 capsules per day with food. A suggested schedule is 2 capsules taken in the morning with food and 2 capsules in the evening with food but participants are able to vary the timing to once daily with food according to preference and ease of use.

Dispensing must be performed by an authorised member of site staff as delegated on the trial Pharmacy Authorised Personnel Log. All dispensed trial IMP must be recorded on the trial Accountability and Dispensing Log.

Courier delivery of IMP is permissible for participants who are unable to return to collect IMP from the dispensing hospital after Visit 2 due to the excessive distance between home and

hospital. The IMP delivery will be arranged by a member of the site staff, who will be responsible for arranging a courier and confirming successful delivery to the participant. Courier account and contact details will be provided by CTRU. Receipt of the IMP by the participant should be documented in the participant's clinical notes. The number of unused capsules should be determined during the telephone assessment and recorded on the case report form (CRF) for the purpose of documenting treatment compliance.

11.4 Storage

Trial IMPs will be stored in pharmacy at room temperature. If the pharmacy storage temperature exceeds 25°C please quarantine stock and contact CTRU.

The supply of trial IMPs (IPE and placebo) must not be used for any purpose other than that outlined in this protocol and should be clearly ring-fenced from standard hospital stock.

11.5 Reconciliation

Receipt of IMP at participating centres and trial stock dispensed to participants must be recorded on the EMT2 Accountability and Dispensing Logs. These completed logs will be returned to CTRU upon request to facilitate central IMP reconciliation.

Participants should return any unused trial IMP stock to the participating centre and the pharmacy should record these returns. The returned capsules should be counted, recorded and the record returned to CTRU prior to local destruction as per standard operating procedures. For participants receiving a courier delivery of IMP, unused capsules will be collected and returned to the dispensing pharmacy at Visit 10/Exit visit or sooner if the participant stops treatment or withdraws from trial treatment and follow up.

Code-break envelopes for any un-dispensed trial IMP will be returned to CTRU during reconciliation for each trial IMP batch. Code-break envelopes for dispensed trial IMP will be collected after all participants have completed the 60-day post-treatment period at the completion of trial treatment. Code-break envelopes will be checked by the CTRU for potential unreported unblinding (i.e. opened or damaged envelopes).

12. Treatment

The following section of the protocol describes treatment for participants with IPE or placebo. The local Investigator, the site pharmacist, other members of the site staff involved with the trial, and the participants themselves, will remain blinded to the treatment allocation (except when emergency unblinding is required).

12.1 Treatment Details

Participants will be randomised to receive either IPE or placebo capsules for a minimum of 2 years and a maximum of 4 years post liver resection. Participants will be resupplied with IMP at each trial visit, as required. Since IMP will be dispensed at each visit/telephone call, it is expected that the participant may eventually accumulate sufficient IMP to last until the next trial visit and a dispensing will not be required. It is the responsibility of the prescribing healthcare professional to determine whether the participant has sufficient IMP with an appropriate expiry date to miss a dispensing visit.

When dispensing IMP at trial visits/telephone calls, authorised members of staff at the participating centre will access the CTRU 24-hour service which will inform the site of the kit-code for the box to be dispensed. Pharmacy will receive a fax or email to inform them of which kit-code labelled box to dispense.

12.2 Treatment Regimen

Participants will be randomised to receive either 4 x 1g capsules of IPE or 4 identical placebo capsules daily. Participants should take their capsules with food.

The trial treatment should be taken daily from the date of randomisation until the participant has completed study treatment (maximum of four years treatment post liver resection).

Trial treatment will continue following diagnosis of disease progression or diagnosis of a new primary cancer as there is still potential for EPA treatment to improve outcomes of any new or recurrent cancer.

12.2.1 Treatment breaks

While it is preferred that participants continue their trial medication daily, it may be necessary for participants to take one or more treatment breaks during follow-up. Examples of possible reasons for a treatment break include in-patient hospital stays (eg. for CRCLM surgery) if nil by mouth is specified or during chemotherapy treatment or other concurrent treatment that results in a persistent adverse reaction (AR) or difficulty taking IMP.

In the event of a persistent AR, a dose reduction (see Section 12.2.4) should be tried prior to a treatment break. Details of any dose reduction or break in treatment should be recorded on the Treatment CRF, including the duration and reason.

12.2.2 Concomitant medication

It is expected that a proportion of participants will require chemotherapy following CRCLM surgery. It is not considered necessary for trial treatment to be discontinued during

chemotherapy. However, should the participant experience adverse events (AEs) during chemotherapy that might be exacerbated by EPA use and these do not resolve with the IPE dose–reduction algorithm (see Figure 1 in Section 12.2.4), the participant may take a temporary treatment break from trial treatment. Details of this treatment break should be recorded on the Treatment CRF.

Details of any concomitant medication, including details of all over-the-counter medications, should be recorded on the Treatment CRF.

Over-the-counter or prescribed nutritional supplements containing any O3FA eg. Seven Seas® or prescribed O3FAs (Vazkepa, Omacor) are **prohibited** while participants are receiving trial treatment and are an exclusion criterion for the trial. Therefore, any participants consistently using over-the-counter O3FA preparations or requiring treatment with a prescription O3FA for hypertriglyceridaemia or for vascular prophylaxis will be withdrawn from trial treatment and the site will complete the Protocol Violation CRF and forward this to CTRU as soon as possible. The participant will continue to be followed up as normal.

As participants are not informed of their treatment allocation, it is possible that any concomitant O3FA supplementation could add to their treatment dose which is not advised in the interest of participant safety. In addition, persistent use of over-the-counter O3FAs may compromise the trial results should participants in the placebo arm receive O3FAs, as this will result in 'contamination' of the control group.

Participants should be reminded at each trial visit/telephone call that it is not permitted for O3FA supplements to be taken during trial participation.

Concomitant use of aspirin and/or any other anti-platelet agent is allowed with usual management of anti-platelet agent use around interventional procedures being followed. Similarly, concomitant warfarin use is allowed with usual careful monitoring of anticoagulation control. In the absence of any data on any adverse interaction between O3FAs and new oral anticoagulants (NOACs) such as rivaroxaban and dabigatran, concomitant use of NOACs is allowed. In the REDUCE-IT trial of 8179 individuals with cardiovascular disease or risk factors (approximately 10% taking concomitant anticoagulation, with or without an antiplatelet agent), serious bleeding events were reported more frequently in subjects receiving IPE 4 g daily (3.4%) than in those receiving placebo (2.6%) when administered in combination with concomitant antithrombotic medication, but occurred at the same rate (0.2%) in subjects not taking concomitant anticoagulant/antiplatelet medication[54].

12.2.3 Known Toxicities

As this is a blinded trial, adverse events should be assessed for causal relationship assuming the participant has been receiving active IPE.

Refer to the Reference Safety Information (RSI) contained within the current approved version of the IB held in the Investigator Site File.

The RSI is located in section 8.4 of the EMT2 Icopsapent Ethyl Investigator Brochure

12.2.4 Dose reduction

Participants should be advised to contact the relevant research nurse between the 6-monthly clinic visits/telephone calls in the event of a persistent AE that may require capsule dose reduction.

In the event that the participant experiences AEs that the treating clinician suspects to be related to trial treatment, the clinician should review the participant's treatment regimen (eg. have the capsules been taken with food?).

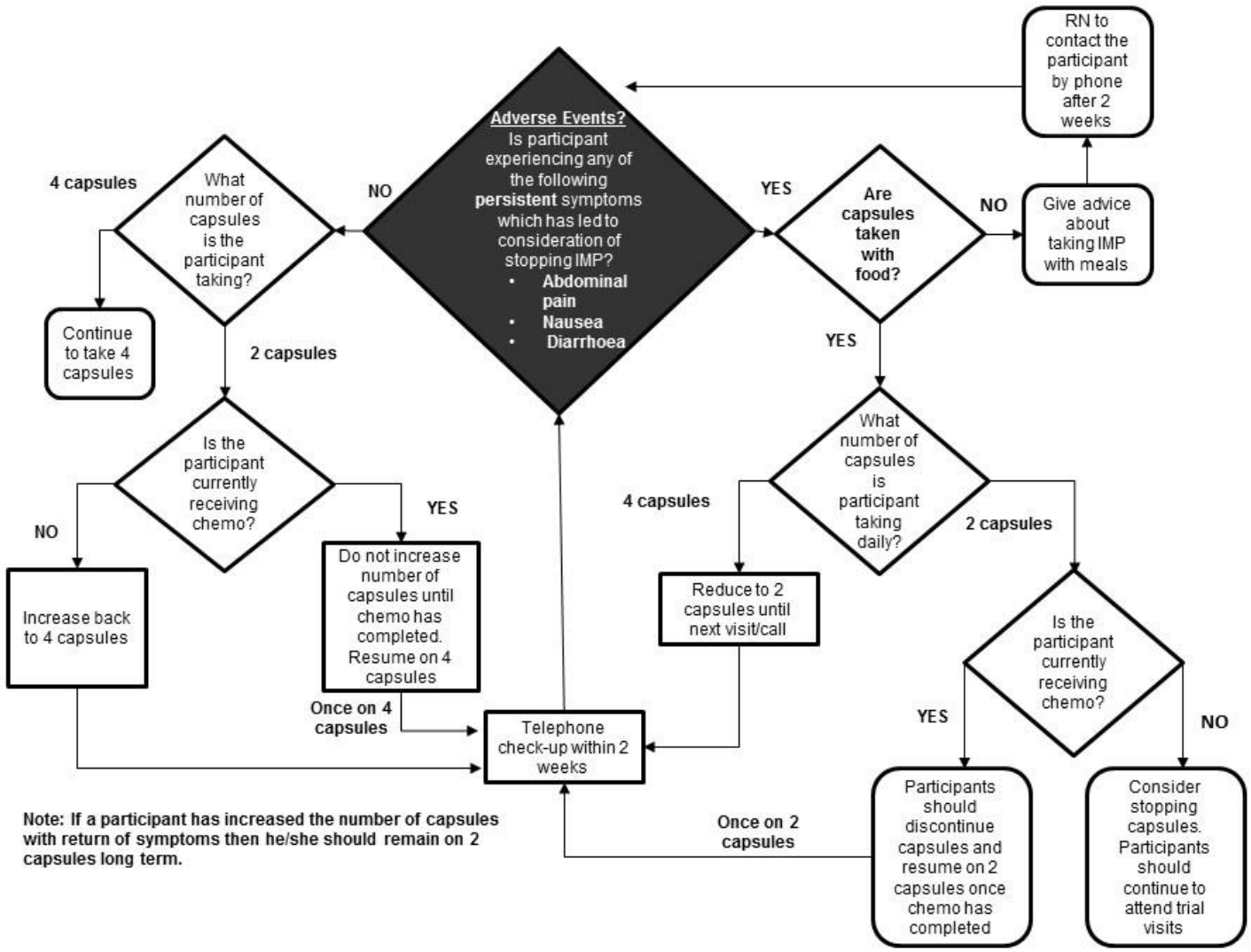
If the AE persists, the dose of trial treatment should be temporarily reduced as per the dose reduction algorithm in Figure 1 below. Dose reduction should be recorded in the medical notes and on the Treatment CRF.

If a participant is undergoing a course of chemotherapy and a dose reduction has stopped the symptoms of an AE, the dose should not be increased back to full dose until the course of chemotherapy has completed.

If a participant is undergoing a course of chemotherapy and has stopped taking trial capsules due to an AE (i.e. is on a treatment break), the participant should resume on the reduced dose once the course of chemotherapy has completed with a view to increasing the capsule dose to 4 capsules daily, in due course. A decision to permanently stop trial treatment should not be made during chemotherapy if possible.

If a participant is still experiencing symptoms of the AE following a dose reduction, is <u>not</u> undergoing a course of chemotherapy and no other factors are considered to be contributory, a permanent halt to trial treatment should be considered. If a participant does permanently stop trial treatment, a Withdrawal CRF should be completed and returned to CTRU within 24 hours. The participant should continue to attend trial visits or take a trial specific telephone call as per the trial visit schedule.

Figure 1: Dose reduction algorithm



12.2.5 Treatment Compliance

Treatment compliance will be assessed by questions at each trial visit/telephone call to determine if the participant has had any delayed, missed or modified doses. This information will be recorded on the appropriate Follow-up Form. Any unused **expired** capsules will be collected from the participants by the research team at the next trial visit or at the end of the trial for those participants undertaking telephone clinic follow up and returned to pharmacy for drug reconciliation and local destruction (see Section 11.5 above for further details).

The fatty acid analysis on visit 2 and 3 samples compared with baseline visit 1 (see Section13.15) will act as a marker of compliance to IPE and also allows the assessment of whether the placebo arm has been 'contaminated' by possible participant supplementation with over-the-counter O3FA.

12.3 Blinding

The Principal Investigator, participating centre staff, pharmacy staff, participants and the CTRU staff involved in the day to day activities of the trial will be blinded to the treatment allocation of each participant.

Participants will not be informed of their trial allocation until the final analysis has been completed and the results of the study are published. At this time the CTRU will provide each site with a list of treatment allocations for participants recruited at that site. Participants cannot request their trial allocations until this time.

The following controls will be employed to maintain the double blind status of the trial:

- The IPE and placebo capsules and bottles will be identical in appearance and have the same labelling.
- Boxes will be identified by a unique kit code assigned at random. The CTRU Safety Statistician (an independent CTRU statistician responsible for carrying out tasks requiring access to unblinded information) will be responsible for maintaining this list, which will be securely password protected when treatment information is contained within the list.
- The Investigator and other members of the site staff involved with the trial and the participants themselves will remain blinded to the treatment allocation (except where emergency unblinding is necessitated).

The following outlines how unblinding will be kept to a minimum for tasks to be conducted unblinded at the CTRU:

- Management of kit-codes on the kit logistics application which is linked to the 24-hour randomisation system will be conducted by the CTRU Safety Statistician in addition to maintaining the back-up kit-code lists for each centre.

- Any unblinded interim reports provided to the Data Monitoring and Ethics Committee (DMEC) will be provided by the CTRU Safety Statistician and the reports will be securely password-protected.

- Suspected Unexpected Serious Adverse Reactions (SUSARs) will be unblinded by the CTRU Safety Statistician. If the event requires expedited reporting, the Safety Statistician will pass the SUSAR to the trial Data Manager who will be responsible for electronic SUSAR reporting to the Medicine and Healthcare Regulatory Agency (MHRA) and the ethics committee. Unblinded records of SUSARs reported will be maintained by the Safety Statistician.

Code break procedures are outlined below in Section 12.3.1 and described in detail in the Emergency Unblinding SSOP provided in the Investigator Site File and Pharmacy Site File.

12.3.1 Emergency Unblinding

Whilst the safety of participants in the trial must always take priority, maintenance of the blind is crucial to the integrity of the trial. Investigators should only break the blind when information about the participant‘s trial treatment is clearly necessary for the appropriate medical management of the participant and where stopping the blinded medication is not sufficient.

Unblinding may be requested on the grounds of safety by the Chief Investigator (CI), local PI or treating physician. It is anticipated that requests for unblinding will most likely originate from a participant, carer (or friend/family member) or personal physician (e.g. GP) at the time of an adverse event or planned change in non-trial related drug therapy. Requests for unblinding will first be handled by the local PI or delegate who will explore the reason for the request and evaluate the importance of knowledge of treatment assignment for participant safety. In the event of a Serious Adverse Event (SAE), all participants should be treated as though they are receiving the active medication. Refer to protocol Section 14 (Pharmacovigilance).

Should an alternative to unblinding not be identified, and if unblinding is required to optimise medical management of the participant, investigators should follow the emergency unblinding process.

Emergency unblinding is provided by the CTRU during Office Hours and the participating site pharmacy at all other times, thereby covering each 24-hour period. It is encouraged that requests for Emergency unblinding should be made directly with CTRU wherever possible.

During Office Hours (9:00 to 17:00 Monday to Friday excluding public/bank holidays, the period between Christmas Eve and New Year, Thursday afternoon before Good Friday and all Tuesdays following a bank holiday except for Mayday and New Year's Day), Investigators should telephone CTRU who will carry out the unblinding procedure.

Outside of Office Hours, or where the Investigator is unable to contact CTRU, emergency unblinding may also be undertaken by contacting the local/assigned pharmacy department at the respective participating centre who will also hold code-break envelopes. Code-Break envelopes for unblindings will be provided to pharmacy at the time of IMP delivery and each envelope will be linked to a specific box of capsules using a unique kit-code.

Direct line for CTRU emergency unblinding: 0113 343 4930

The following information will be needed to perform an emergency unblinding:

- Participant details, including trial ID number, initials and date of birth
- Name of trial research site and site code
- Name of person making the request for a code-break
- Reason for requesting a code-break
- Confirmation of whether the PI authorised the request

Following the emergency unblinding of a participant, CTRU will fax or send via secure email a confirmation of emergency unblinding to the requester and the local PI. The details of the emergency unblinding should be recorded on the EMT2 Unblinding Log provided by CTRU.

Outside of Office Hours, or where the Investigator or treating physician is unable to contact CTRU, emergency unblinding must be performed by the local pharmacy department. The responsible pharmacist on duty will complete the Unblind Request CRF, retrieve the code-break information and reveal the treatment allocation to the person requesting the unblind. The pharmacist must return (by fax or secure email) the completed Unblind Request CRF to the CTRU within 24 hours of the unblinding request.

Following an emergency unblinding the participant should stop trial treatment and be treated in line with local hospital policy. The participant will continue to be followed-up as per the trial protocol.

Further information on emergency unblinding can be found in the Emergency Unblinding SSOP located within the Investigator Site File and Pharmacy Site File.

12.4 Withdrawals

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants withdrawn from treatment or prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and CRFs will continue to be completed.

The Withdrawal CRF should be completed and faxed or sent via secure email to the CTRU **within 24 hours** of the research team becoming aware.

Treatment breaks are permitted if necessary (see Section 12.2.1). Participants should not be recorded as withdrawn from trial treatment until it is clear that they will not be resuming trial treatment.

The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

It should be made clear to any participant specifically withdrawing consent for further data collection that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

13. Assessments, Samples and Data Collection

Data will be collected using paper CRFs, the electronic templates for which will be provided by the CTRU and upon completion should be returned to the CTRU at the University of Leeds. Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial in the Investigator Site File.

The timings of interventions and assessments required for the EMT2 trial are summarised in Appendix A: Schedule of Events.

13.1 Assessment of eligibility and randomisation

Potential participants will be identified through the hepatobiliary MDT at the time of the decision to offer CRCLM surgery to that individual. The MDT will review the most recent CT of the

thorax, abdomen and pelvis and determine eligibility for CRCLM surgery. This CT scan may be collected retrospectively as part of the sarcopaenia analysis.

If the patient is eligible for CRCLM surgery, the surgeon will assess eligibility (medical review including medical history, assessment of management of the underlying disease, pregnancy and concomitant medication use) for trial participation at the surgical outpatient visit at which CRCLM surgery is discussed with the patient. The trial site team may telephone the potential participant in order to introduce the trial in general terms and then send a PIS/ICF in advance of an outpatient clinic appointment, especially if the time between outpatient review of eligibility for surgery and the date of CRCLM surgery is limited.

Participants must be screened and have given written informed consent before any trial specific procedures are performed and the participant is randomised.

For patients who do not go on to be registered, details should be added to the Screening Log (see Section 10.2). All patients who consent to trial participation must be registered.

If, following randomisation, a participant is found to be in breach of the eligibility criteria the Protocol Violations CRF should be completed and returned (by fax or secure email) to CTRU immediately.

13.2 Visit 1: Baseline Assessment and Data Collection

Trial specific assessments must take place following consent and randomisation, except for the baseline Quality of Life questionnaires which must be done following consent but should wherever possible be done **before** meeting with the clinician/randomisation.

Once randomised into the study, the participant will be assessed by a member of the research team and the following baseline assessments will be carried out:

- Participant self-reported assessments: the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 Quality of Life questionnaires and a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 1 Pack.
- Participants should be provided with a Participant Diary Booklet to record information over the next visit period. The information collected in the booklet will be the information to be collected in the health economics questionnaire and details on compliance and adverse events. The booklet is intended to act as a reminder to the participant and must not be handed in to clinic or returned to the CTRU.
- Weight in kilograms (in light indoor clothing and without shoes).
- Blood sample for red blood cell fatty acid analysis (**for Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust only**). A blood sample should be collected in two EDTA-coated Vacuette® tubes and agitated

immediately to prevent clotting. The blood components should be separated within 30 minutes of taking the blood sample (see Section 13.15). If not processed immediately, store the two tubes in the fridge at 4°C for up to 30 minutes.

- One box of IMP will be dispensed.
- A CT scan should be organised for 6 months following the anticipated date of CRCLM surgery, once known. For participants undergoing a two-stage resection, the CT scan should be planned for 6 months following the completion of the second resection.
- An invitation to join the Biospecimen Collection sub-study should be extended to the participant using the dedicated PISICF (see Biospecimen Collection protocol).
- If written informed consent for the Biospecimen Collection sub-study is obtained, sample collection packs should be provided and a blood sample taken (if consent given) according to the Biospecimen Collection protocol.

13.3 Research nurse telephone calls (every 2 weeks between visits 1 and 2)

Participants will be contacted every 2 weeks +/-3 days by a research nurse between randomisation and CRCLM surgery. If the research nurse is unable to contact the participant every reasonable effort will be made to contact the participant as soon as possible. The research nurse will contact the participant by telephone to perform the following assessments:

- Toxicity assessment: collection of any adverse events which may have occurred over the last two weeks.
- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).
- Treatment compliance: the participant will be asked if they have missed any treatment doses in the last two weeks and for what reason.
- Details of concomitant medications including over-the-counter O3FA supplements since visit 1 or since the last research nurse telephone call. Participants should be reminded that over-the-counter O3FA supplements are prohibited.

13.4 Visit 2: CRCLM surgery, Treatment Assessments and Data Collection

Participants will have a trial visit during admission on the first day of the hospital inpatient stay for CRCLM surgery. The CRCLM surgery should be <6 weeks from post randomisation.

The following assessments will be carried out:

- Toxicity assessment: collection of any adverse events which may have occurred since the last research nurse telephone call.
- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).
- Participant self-reported assessments: a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 2 Pack. It is preferable that this is administered to the participant before surgery but if this is not possible within the timeframe pre-surgery, the Visit 2 Pack may be completed during the inpatient stay.
- Participants should be provided with a Participant Diary Booklet to record information over the next visit period. The information collected in the booklet will be the information to be collected in the health economics questionnaire and details on compliance and adverse events. The booklet is intended to act as a reminder to the participant and must not be handed in to clinic or returned to the CTRU.

- Weight in kilograms (in light indoor clothing and without shoes). This may be taken from the pre-operative assessment in the clinical records.

- Blood sample for red blood cell fatty acid analysis (for Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust only). **Please note that it is preferable that the blood sample is obtained prior to surgery, ideally on admission to hospital.** A blood sample should be collected in two EDTA-coated Vacuette® tubes and agitated immediately to prevent clotting. The blood components should be separated within 30 minutes of taking the blood sample (see Section 13.15). If not processed immediately, store the two tubes in the fridge at 4°C for up to 30 minutes.

- See Biospecimen Collection protocol if participant is in this sub-study.

- Treatment compliance: the participant will be asked if they have missed any treatment doses since the last research nurse telephone call and for what reason.

- Details of concomitant medications including over-the-counter O3FA supplements since the last research nurse telephone call. Participants should be reminded that over-the-counter O3FA supplements are prohibited.

- The IMP dispensed at visit 1 should be checked regarding the expiry date and the participant should be advised to use the IMP box currently in use before opening the IMP box dispensed at visit 2.
- One box of IMP should be dispensed if necessary.

- In the event that the liver metastases are not able to be removed surgically and macroscopic disease remains, a CT scan should be arranged as soon as possible in order to measure the existing disease. Trial treatment and follow-up should continue as per protocol.

13.5 Visit 3: Treatment Assessments and Data Collection

Participants will have a trial visit 6 months +/- 2 weeks after the date of CRCLM surgery. For those participants having adjuvant chemotherapy the CT scan may be during the chemotherapy treatment period to ensure that the trial visit at 6 months +/- 2 weeks can be adhered to. For all participants the following assessments will be carried out:

- Clinical evaluation to assess for disease progression and new primary cancer, as per local standard practice.

- Toxicity assessment: collection of any adverse events which may have occurred since the last trial visit.

- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).

- Participant self-reported assessments: the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 Quality of Life questionnaires and a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 3-10 Pack. Questionnaires should be completed by participants at the time of clinical assessment, but before discussion of the outcome of any medical assessments or blood tests wherever possible.

- Participants should be provided with a Participant Diary Booklet to record information over the next visit period. The information collected in the booklet will be the information to be collected in the health economics questionnaire and details on compliance and adverse events. The booklet is intended to act as a reminder to the participant and must not be handed in to clinic or returned to the CTRU.

- Weight in kilograms (in light indoor clothing and without shoes).

- CT scan of thorax, abdomen and pelvis.

- Treatment compliance: the participant will be asked if they have missed any treatment doses since the last trial visit and for what reason.

- Details of concomitant medications including over-the-counter O3FA supplements since the last trial visit. Participants should be reminded that over-the-counter O3FA supplements are prohibited.

- Blood sample for red blood cell fatty acid analysis (for Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust only). A blood sample should be collected in two EDTA-coated Vacuette® tubes and agitated immediately to prevent clotting. The blood components should be separated within 30 minutes of taking the blood sample (see Section13.15). If not processed immediately, store the two tubes in the fridge at 4°C for up to 30 minutes.

- See Biospecimen Collection protocol if participant is in this sub-study.

- One box of IMP will be dispensed.
- The IMP dispensed at visit 2 should be checked regarding the expiry date and the participant should be advised to use the IMP box currently in use before opening the IMP box dispensed at visit 3.

For Visit 3 and all subsequent trial visits, follow-up can be on a remote basis by telephone interview, QoL questionnaires posted and courier delivery of IMP, if participants are unable to attend the recruiting hospital for repeat visits. Clinical evaluation, toxicity assessment, compliance and concomitant medication assessment, as well as determination of hospital resource activity, will be performed by telephone. Self-reported weight will be obtained. IMP will be delivered to the participant's postal address (see Section 11.3). CT scanning will be performed by the local Oncology team as per usual surveillance guidelines. Participants randomised in Leeds and Sheffield, but undergoing remote follow-up, will not be expected to provide blood samples for Visit 3.

13.6 Visits 4-6: Treatment Assessments and Data Collection

Participants will have a trial visit at 12, 18 and 24 months (+/- 2 weeks) after the date of CRCLM surgery. The following assessments will be carried out at each visit:

- Clinical evaluation to assess for disease progression and new primary cancer, as per local standard practice.

- Toxicity assessment: collection of any adverse events which may have occurred since the last trial visit.

- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).

- Participant self-reported assessments: the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 Quality of Life questionnaires and a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 3-10 Pack. Questionnaires should be completed by participants at the time of clinical/telephone assessment, but before discussion of the outcome of any medical assessments or blood tests wherever possible.

- Participants should be provided with a Participant Diary Booklet to record information over the next visit period. The information collected in the booklet will be the information to be collected in the health economics questionnaire and details on compliance and adverse events. The booklet is intended to act as a reminder to the participant and must not be handed in to clinic or returned to the CTRU.

- Weight in kilograms (in light indoor clothing and without shoes).

- CT scan of thorax, abdomen and pelvis.

- Treatment compliance: the participant will be asked if they have missed any treatment doses since the last trial visit and for what reason.

- Details of concomitant medications including over-the-counter O3FA supplements in since the last trial visit. Participants should be reminded that over-the-counter O3FA supplements are prohibited.

- One box of IMP will be dispensed.

- The IMP dispensed at the previous visit should be checked regarding the expiry date and the participant should be advised to use the IMP box currently in use before opening the IMP box dispensed at this visit/telephone call.

- See Biospecimen Collection protocol if participant is in this sub-study. A sample collection pack may need handing /posting to the participant at visit 5.

See Section 13.5 for details of remote follow-up for Visits 4-6.

13.7 Visits 7-9: Treatment Assessments and Data Collection

Participants should have a trial visit at 30, 36 and 42 months (+/- 2 weeks) after the date of CRCLM surgery. The following assessments will be carried out at each visit:

- Clinical evaluation to assess for disease progression and new primary cancer, as per local standard practice.

- Toxicity assessment: collection of any adverse events which may have occurred since the last trial visit.

- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).

- Participant self-reported assessments: the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 Quality of Life questionnaires and a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 3-10 Pack. Questionnaires should be completed by participants at the time of clinical assessment, but before discussion of the outcome of any medical assessments or blood tests wherever possible.

- Participants should be provided with a Participant Diary Booklet to record information over the next visit period. The information collected in the booklet will be the information to be collected in the health economics questionnaire and details on compliance and adverse events. The booklet is intended to act as a reminder to the participant and must not be handed in to clinic or returned to the CTRU.

- Weight in kilograms (in light indoor clothing and without shoes).

- CT scan of thorax, abdomen and pelvis at visit 8 only: CT scans are carried out on an annual basis after 2 years post CRCLM surgery.

- Treatment compliance: the participant will be asked if they have missed any treatment doses since the last trial visit and for what reason.

- Details of concomitant medications including over-the-counter O3FA supplements since the last trial visit. Participants should be reminded that over-the-counter O3FA supplements are prohibited.

- One box of IMP will be dispensed.

- The IMP dispensed at the previous visit should be checked regarding the expiry date and the participant should be advised to use the IMP box currently in use before opening the IMP box dispensed at the most recent visit.

- See Biospecimen Collection protocol if participant is in this sub-study. A sample collection pack may need handing /posting to the participant at visit 7.

See Section 13.5 for details of remote follow-up for Visits 7-9.

13.8 Visit 10/Exit Visit: Treatment Assessments and Data Collection

Participants will have the trial visit no later than 48 months (+/- 2 weeks) after liver resection surgery. The trial will complete the interventional phase 2 years after the last participant is randomised. At this point, participants will require an exit visit which may be less than 6 months since their last trial visit: in this case the visit should be within 2 months of the end of the interventional phase (this may be the standard clinic follow-up visit if timing is appropriate).

The following assessments will be carried out at the visit:

- Clinical evaluation to assess for disease progression and new primary cancer, as per local standard practice.
- Toxicity assessment: collection of any adverse events which may have occurred since the last trial visit.
- Details of hospital resource activity (e.g. hospital inpatient stays, outpatient clinics attending, accident and emergency attendances).
- Participant self-reported assessments: the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 Quality of Life questionnaires and a health economics questionnaire will be administered to the participant in a Participant Questionnaire Visit 3-10 Pack. Questionnaires should be completed by participants at the time of clinical assessment, but before discussion of the outcome of any medical assessments or blood tests wherever possible.
- Weight in kilograms (in light indoor clothing and without shoes).
- CT scan of thorax, abdomen and pelvis.
- Treatment compliance: the participant will be asked if they have missed any treatment doses since the last trial visit and for what reason.
- Details of concomitant medications including over-the-counter O3FA supplements since the last trial visit.
- The IMP dispensed at any previous visit should be returned to pharmacy. For those who have undergone remote follow-up, arrangements will be made for the trial courier to collect all unused IMP.
- See Biospecimen Collection protocol if participant is in this sub-study. A sample collection pack may need handing /posting to the participant at visit 10.

13.9 60 days post-treatment telephone call

Participants will be contacted 60 days after the participant's exit visit. The research nurse will contact the participant by telephone to perform the following assessments:

- Toxicity assessment: collection of any adverse events which may have occurred over the last 60 days.

13.10 End of Trial Treatment

Participants should continue on trial treatment following diagnosis of disease progression or diagnosis of a new primary cancer.

The interventional phase of the trial will complete 2 years after the last participant is randomised. At the end of the interventional phase, participants will be requested to attend clinic for an 'Exit Visit' which should be within 2 months of the end of the interventional phase (this may be the standard clinic follow-up visit if timing is appropriate).

Participants should return all unused IMP upon cessation of trial treatment either at a hospital visit or via a courier.

13.11 Disease Progression

The date of clinical progression is defined as the **date of the CT scan or the relevant assessment at** which disease progression or new recurrence is identified. This can be clinical progression or, for RECIST evaluable disease, radiological progression by RECIST principles.

In the event that the liver or extra-hepatic metastases are found to be unable to be resected following randomisation (macroscopic disease remaining), a CT scan to determine the existing disease should be carried out as soon as possible following surgery. This scan will act as a baseline for assessment of progression and should be reported in accordance with RECIST v1.1[56] (see Appendix D). Subsequent scans to monitor disease progression should also be reported in accordance with RECIST v1.1.

Up to 5 target lesions should be defined. Disease progression is defined as:

- Appearance of one or more new lesions
- A minimum 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Clear, unequivocal progression of non-target lesions (which may be measurable or non-measurable)

In the event that a participant is found to have positive microscopic margins following liver resection (microscopic disease) an immediate CT scan is not required as this disease is not evaluable according to RECIST. Disease progression is defined as the appearance of CRC metastases by CT scan of the thorax/abdomen/pelvis.

Disease progression in the extra-hepatic metastases will be assessed using the CT scan of the thorax/abdomen/pelvis if appropriate. Other clinical evaluations will be carried out to monitor extra-hepatic metastases as required and as per local standard practice.

In a small number of cases, participants may have clear clinical symptoms of disease progression without confirmatory imaging. In this circumstance, clinical deterioration that is unambiguously due to CRC progression should be reported as a progression event and the date of clinical assessment should be recorded as the date of clinical progression.

13.12 Quality of Life

For all participants, Quality of Life (QoL) questionnaires will be completed at visit 1, visit 3 and at all clinic visits thereafter. The QoL questionnaires include the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 questionnaires.

13.12.1.1 Timing and administration of Quality of Life questionnaires

Participants will be asked to complete the Quality of Life questionnaires prior to receiving their first box of capsules and wherever possible prior to meeting with the clinician at the clinic visit (or prior to randomisation at visit 1). The Visit 1 Questionnaire Pack should be given to participants after consent has been obtained and eligibility has been confirmed. All questionnaires will be provided in clinic or by post.

Questionnaires should be completed by participants at the time of clinical assessment, but before discussion of the outcome of any medical assessments or blood tests wherever possible. Participants will be asked to seal the questionnaires in pre-supplied envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the CTRU for entry into the database.

13.13 Health Economics

For all participants, a health economics questionnaire will be completed at all clinic visits.

13.14 Cachexia CT measurements

Changes in lean body mass will be measured longitudinally from the routine CT abdomen images from participants in Leeds and Sheffield using the method of Baracos (based on muscle area at the L3 vertebral level[44]). The routine CT scans will be obtained at baseline (confirmation of eligibility), visit 3 and visit 4. The CT scan images will be requested at the end of the interventional phase, depending on the availability of funding for measurement of this exploratory endpoint. These measurements could easily be extended to cover longer periods of follow-up or expanded to include participants at other sites if funding is available.

It is the responsibility of the participating centre to obliterate all personal identifiable data prior to sending the CT scan to the CTRU/central reviewer. The trial number, date of birth and initials will be used to identify the participant.

13.15 Red Blood Cell Fatty Acid Analysis

Blood samples taken at visits 1, 2 and 3 will be collected from participants recruited at two of the participating centres: Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust. These samples will be analysed to measure the red blood cell fatty acid content which determines the absolute and relative content of the major O3FAs including EPA, as well as the EPA/AA and EPA+DHA/AA ratio[52].

The fatty acid analysis on the baseline samples (see Section 13.2) will enable the investigation of whether O3FA status predicts subsequent therapeutic response to IPE. The absolute and differential O3FA levels at visits 2 and 3 will also act as a marker of compliance to IPE and allows the assessment of whether the placebo arm has been 'contaminated' by possible participant supplementation with over-the-counter O3FA.

At visits 1-3, whole blood will be collected in EDTA tubes for centrifugation and isolation of plasma and red blood cells. Both fractions will be stored locally at -30°C before courier transport of the complete sample sets to the Institute of Cancer Therapeutics (ICT), University of Bradford which will act as the central biobank. Lipid extraction from red blood cells followed by derivatisation and liquid chromatography-tandem mass spectrometry (LC-MS/MS) measurement of individual fatty acid (FA) species will be performed as described in the EMT2 Lab Manual[52].

The red blood cell fatty acid analysis will be carried out centrally at the Institute of Cancer Therapeutics (ICT), University of Bradford.

The fatty acid analysis will be carried out on blood samples from all participants recruited at Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust only.

At visits 1-3, whole blood will be collected for centrifugation and isolation of plasma and red blood cells. Blood samples will be obtained using the BD Vacutainer® system, following local Trust practice. Two purple cap K_2EDTA 6ml tubes will be filled to capacity. Tubes should be agitated immediately to prevent clotting.

The blood components should be separated within 30 minutes of taking the blood sample. If not processed immediately, the two K2EDTA Vacutainer tubes should be stored in the fridge at 4°C for up to 30 minutes.

Separation of blood components will be achieved by centrifugation of the sample in K_2EDTA Vacutainers in a centrifuge, preferably refrigerated.

Full details on the separation of the blood components are provided in the EMT2 Lab Manual.

All separated fractions will be stored locally at -30°C before courier transport of the complete sample sets to the ICT, Bradford every three months. Lipid extraction from red blood cells followed by derivatisation and liquid chromatography-tandem mass spectrometry (LC-MS/MS) measurement of individual FA species will be performed as described in the EMT2 Lab Manual.

The fatty acid-analysis may be carried out at intervals during the two years of recruitment in order to assess treatment compliance and/or 'contamination' by 'over-the-counter' O3FA use.

Any blood samples remaining following analysis for trial purposes will be stored at the Institute of Cancer Therapeutics at the University of Bradford and may provide a resource for future studies in colorectal cancer. Ethical approval will be obtained for any future studies involving EMT2 data or samples and the Institute of Cancer Therapeutics at the University of Bradford has been granted a main HTA licence (12191). Participants will not be identified in the results of future studies.

It is the responsibility of the participating centre to ensure that samples are appropriately labelled in accordance with the trial procedures to conform with the 1998 Data Protection Act. Blood samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

13.16 Biospecimen Collection, storage and transport

Please see the Biospecimen Collection protocol for details of sample collection and transport. The use of a barcode identifier linked to the EMT2 trial participant number and date of the sample means that all samples will be stored, transported and analysed in an nonymised but linked manner.

13.17 Adverse Events and Serious Adverse Events

Adverse Events (AEs) and Adverse Reactions (ARs) will be collected at all trial clinic visits and by 2-weekly telephone calls between visit 1 and visit 2 and at 60 days post visit 10/exit visit. AEs and ARs will be collected on the CRFs. These should be reported via the standard data management routes and expedited reporting is not required.

Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected from randomisation until 60 days after the last trial IMP was taken.

For all SAEs, SARs and SUSARs occurring in the trial, an SAE or SAR Report CRF must be completed and faxed or sent via secure email to the CTRU **within 24 hours** of the site becoming aware of the event (see Pharmacovigilance Section 14).

Please see Appendix B for details on the Pharmacovigilance reporting procedures.

13.18 Pregnancies

Although non-clinical studies have demonstrated no reproductive or developmental toxicity relating to EPA supplementation, there have been no formal studies on the effect of EPA on human reproductive or developmental toxicity. Therefore women of childbearing age and men with partners of childbearing potential must use effective contraceptive measures for the duration of trial treatment and for 60 days following permanent cessation of trial treatment.

All pregnancies and suspected pregnancies (in a trial participant or their partner) occurring from the date of randomisation to the telephone call at 60 days after the end of trial treatment must be reported to the CTRU by completing the Notification of Pregnancy CRF which must be faxed or sent via secure email to the CTRU **within 7 days** of the site becoming aware of the pregnancy.

All trial participants who become pregnant during trial participation must discontinue trial treatment immediately.

The CTRU will report all pregnancies occurring during trial treatment to the Sponsor and all pregnancies will be followed-up until the outcome is known.

13.19 Deaths

All deaths occurring from the date of randomisation to the telephone call 60 days after the end of trial treatment must be recorded on the Notification of Death CRF and faxed or sent via secure email to the CTRU **within 24 hours** of the site becoming aware of the death.

Deaths occurring more than 60 days after the end of trial treatment but during trial follow-up must also be recorded on the Notification of Death CRF but may be returned as per standard data management processes.

13.20 Protocol Deviations and Violations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the CTRU. All such deviations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

13.21 End of Trial

The end of trial is defined as the date of the collection of the last participant's last data item.

13.22 Trial Data and Documentation held at sites

Participating sites must maintain essential trial documentation in an Investigator Site File and a Pharmacy Site File, which will be provided by the CTRU. It is the responsibility of the site staff to ensure these files are properly maintained during the trial and archived according to the Sponsor requirements at the end of the trial (see Section 23 on archiving).

13.23 Case Report Forms (CRFs)

Data will be recorded by site research staff on trial-specific paper CRFs. The originals will be submitted by post to the CTRU within two weeks of the data being collected, and photocopies of the completed CRFs will be held at site. A number of CRFs require expedited reporting to the CTRU:

- Within 24 hours of the research team becoming aware: SAE and SAR CRFs, Death CRFs, Withdrawal CRFs (to the CTRU)

- Within 7 days of the research team becoming aware: Notification of Pregnancy (to the CTRU)

Only the participant's trial number, date of birth and initials will be added to the CRFs. **Participating centre staff are responsible for ensuring the CRFs returned to CTRU do not contain any other personal identifiable data** (with the exception of the participant's NHS number which will be recorded at baseline). Following receipt of the completed CRFs, the CTRU will contact sites to resolve any missing or discrepant data.

It is the responsibility of the site to ensure all photocopies of the completed CRFs are appropriately maintained at site during the trial (including any amendments) and archived according to the Sponsor requirements at the end of the trial (see Section 23 on archiving).

13.24 Safety Monitoring Plan

See Appendix C.

14. Pharmacovigilance

14.1 General Definitions

'**Adverse Event' (AE)** – any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the use of a medicinal product, whether or not considered to be related to the medicinal product.

'Adverse Reaction' (AR) – all untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error and including misuse and abuse of the product).

'Serious Adverse Event' (SAE) – any untoward medical occurrence or effect that at any dose:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- jeopardised the subject or required intervention to prevent one of the above.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have

caused death if it were more severe. Medical and scientific judgement must be exercised in deciding whether an event is 'serious' in accordance with these criteria.

'Serious Adverse Reaction' (SAR) – reference is made to the criterion of 'Seriousness' above in relation to SAE. Where an SAE is deemed to have been related to any IMP used in this trial the event is termed as a serious adverse reaction (Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.)

'Suspected Unexpected Serious Adverse Reaction' (SUSAR) – means an adverse reaction, the nature and severity of which is not consistent with the applicable product information:

- in the case of a product with a marketing authorisation, in the summary of product characteristics for that product,
- in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

14.2 Operational Definitions

Adverse events will be collected for all participants and will be evaluated for intensity and causal relationship with the trial medication or other factors according to the National Cancer Institute (NCI) CTCAE V4.0 (NCI-CTCAE). A copy is provided in the EMT2 Investigator Site File and may also be obtained at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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14.2.1 Adverse Events (AEs) / Adverse Reactions (ARs)

For general definitions of AEs and ARs, please see section 14.1 above. As this is a blinded trial, AEs should be assessed for expectedness and causal relationship assuming that the participant has been receiving IPE 4g daily.

14.2.2 Serious Adverse Events (SAEs) / Serious Adverse Reactions (SARs)

When determining whether an SAE or SAR is expected or not, reference will be made to the approved IPE Investigator Brochure (IB) supplied by the CTRU. The Reference Safety

Information (RSI) by which Serious Adverse Reactions should be assessed is in section 8.4 of the EMT2 Icosapent Ethyl IB.

Participants may receive chemotherapy during trial participation if considered appropriate by the treating clinician. Chemotherapy will be prescribed as per local standard practice and is not a trial intervention. It is not considered necessary for trial treatment to be discontinued during chemotherapy. In the event that the participant experiences an SAE during chemotherapy treatment, it should be assessed whether the event is related to chemotherapy or IPE. If the event is related to chemotherapy, it should be assessed whether the event has been exacerbated by IPE or could possibly have been exacerbated by IPE. Please refer to Appendix B for the Pharmacovigilance Reporting Flowchart.

14.2.2.1 Events <u>not</u> to be classed as SAEs / SARs

The following events will **<u>not</u>** be classed as SAEs / SARs within this trial and will therefore not be subject to expedited reporting:

Hospitalisation for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications;
- Any admission to hospital or other institution for general care where there was no deterioration in condition;
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

14.2.2.2 Events classed as <u>expected</u> SAEs / SARs

Any events which will be classed as expected SAEs / SARs within this trial are given in the RSI (section 8.4 of the current approved EMT2 Icosapent Ethyl IB). Such events will **<u>not</u>** be reportable as SUSARs on the trial, unless the severity of the event is considered to be unexpected. The current approved version of the EMT2 IPE IB must always be referred to.

All events should be reviewed for relatedness by the Principal Investigator, or another medically qualified member of the research team authorised on the EMT2 Authorised Personnel Log. The CI will review all SARs on behalf of the Sponsor in order to determine expectedness.

14.2.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For general definitions of SAEs and SARs, please see Section 14.2.2 above. A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse drug reaction which also demonstrates the following characteristic of being unexpected:

> Unexpected – An adverse event, the nature **OR** severity of which is NOT consistent with the RSI in the current approved version of the EMT2 Icosapent Ethyl IB

SUSARs will be subject to expedited reporting to the Medicines and Healthcare and products Regulatory Authority (MHRA) and Research Ethics Committee.

As this is a blinded trial, serious adverse events should be assessed for expectedness and causal relationship assuming that the participant has been receiving IPE.

Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore expedited reporting. However, where SARs are thought to be associated with placebo (e.g. reaction due to excipient or impurity), the CTRU will forward such cases to the CI for review of causality and expectedness on behalf of the Sponsor and, if appropriate, onward report to the MHRA and REC. Routinely breaking the blind could compromise the integrity of the trial. For this reason blind-breaking will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator would be expected to provide an evaluation on the causality of SAEs as though the participant was receiving the active medication.

14.3 Reporting Requirements

All SAEs/SARs/SUSARs occurring from the time of randomisation until the 60 days post cessation of trial treatment must be recorded on the SAE Form or the SAR Form.

For each SAE or SAR/SUSAR the following information will be collected:

- Full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality(i.e. relatedness to trial drug), in the opinion of the investigator
- whether the event would be considered expected or unexpected

- Principal Investigator signature (or another clinically qualified member of the medical team authorised in the EMT2 Authorised Personnel Log)

For SARs and SUSARs additional information will be collected on concomitant medications, relevant medical history, diagnostic tests and treatment for the event.

All events must be reviewed and assessed (for seriousness and causality) by the Principal Investigator, or another medically qualified member of the research team authorised in the EMT2 Authorised Personnel Log. If an authorised medic is not available on the day the site team become aware of the event, initial reports without causality must still be faxed or sent via secure email to the CTRU **within 24 hours** of the site becoming aware, and must be followed-up by medical assessment as soon as possible thereafter.

SARs must be recorded on the SAR Form and faxed or sent via secure email to CTRU **within 24 hours** of the research staff becoming aware of the event.

Subsequently, follow-up reports (detailing changes in condition or other follow-up information) must be reported to CTRU within 24 hours of the information becoming available. Events will be followed up until the event is resolved or a final outcome has been reached.

SAEs must be recorded on the SAE Form and reported to the CTRU within 24 hours of the trial team becoming aware of the event. SAE data will be reviewed as collated data and will be reviewed for trends by the Chief Investigator at quarterly intervals (in a blinded manner) and by the Data Monitoring and Ethics Committee at six monthly intervals (in an unblinded manner).

It is expected that SAEs, SARs and SUSARs may be identified by the centre at which the participant is receiving chemotherapy (for those participants receiving chemotherapy as per standard practice) which may be different to the randomising centre. It is the responsibility of the chemotherapy team to report events fulfilling the seriousness criteria to the trial team at the randomising centre. An authorised clinician on the trial team is responsible for assessing whether the event is related to trial treatment. If the event is considered to be serious, it is the responsibility of the trial team to report the event to the CTRU **within 24 hours of becoming aware** of the event.

14.3.1 Reporting of Adverse Events (AEs)

All AEs occurring **from randomisation up to 60 days after the end of trial treatment** must be recorded on the appropriate CRF. These are not subject to expedited reporting to CTRU.

14.3.2 Reporting of Adverse Reactions (ARs)

All ARs occurring **from randomisation up to 60 days after the end of trial treatment** must be recorded on the appropriate CRF, which will be posted to CTRU within 2 weeks of the assessment. These are not subject to expedited reporting to CTRU.

14.3.3 Reporting of Serious Adverse Events (SAEs)

All SAEs occurring **from randomisation up to 60 days after the end of trial treatment** (see Section 14.2.2 above for definition) must be recorded on the SAE CRF and sent to the CTRU within 24 hours.

Please ensure that only one event is reported on each SAE CRF (details of multiple symptoms should be listed if they relate to the same event).

Once all resulting queries have been resolved, the original wet-ink CRF will be posted to the CTRU and a copy retained at site.

14.3.4 Expedited Reporting of Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SARs and SUSARs occurring **from randomisation up to 60 days after the end of trial treatment** (see Section 14.2.2 above for definition) must be recorded on the SAR CRF and faxed or sent via secure email to the CTRU **within 24 hours** of the local research team site staff becoming aware of the event (this includes participants who have withdrawn consent for data collection, see Section 12.4). Any SARs or SUSARs which the site team become aware of after this point must still be reported to CTRU.

Once all resulting queries have been resolved, the original wet-ink CRF will be posted to the CTRU and a copy retained at site.

Please ensure that only one event is reported on each SAR CRF (details of multiple symptoms should be listed if they relate to the same event).

14.4 Responsibilities

14.4.1 Principal Investigator:

1. Checking for AEs and ARs when participants attend for treatment / follow-up.

2. Using medical judgement in assigning seriousness and causality using the EMT2 IPE Investigator Brochure approved for the trial.
3. Ensuring that all SAEs, SARs and SUSARs are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs, SARs and SUSARs are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

14.4.2 Chief Investigator (CI) / delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all events assessed as SARs in order to determine expectedness. In the event of disagreement between local assessment and the Chief Investigator (CI), local assessment will not be downgraded but the CI may add comments prior to reporting to MHRA and REC.
4. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).
7. Conduct of the Biospecimen Collection sub-study.

14.4.3 CTRU:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

3. Reporting safety information to the independent oversight committee identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the MHRA, REC and Sponsor within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting.
7. Checking for (annually) and notifying Principal Investigators of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.
9. Notify Amarin Pharma Inc of any SUSARs occurring in trial participants using the CTRU SUSAR CRF. Initials and date of birth will be removed from the CRF before sending to Amarin. Participants will be identified by trial number only.

14.4.4 Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

14.4.5 Data Monitoring & Ethics Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual basis.

15. Participant-reported measures

Quality of life will be assessed by participants' self-reported symptoms and functioning using validated instruments completed by participants at visits 1, 3 and all clinic visits thereafter. All instruments are self-administered to avoid interviewer bias. The three QoL questionnaires and the health economics questionnaire to be used in this study are described below.

The EQ-5D is a well validated, multi-purpose, standard health-related QoL evaluation questionnaire, which will be used to assess generic QoL. It provides a simple descriptive profile and a single index value for health status.

The EORTC QLQ-C30 is a well validated questionnaire developed to assess the quality of life of cancer patients. This information relates to the previous 1-week time period. It is supplemented by disease-specific modules and the colorectal liver metastases module QLQ-LMC21 will also be used in the study. The majority of this information relates to the previous 1-week time period, with information relating to the effect of the disease or treatment on the participants' sex-life relating to the previous 4-week time period.

A participant self-reported questionnaire will be administered at Visit 10/Exit Visit to determine the participant's opinion of their trial treatment allocation at the end of the treatment period. This questionnaire will be used to evaluate the effectiveness of the blinding measures used throughout the trial.

16. Economic Evaluation

The aim of the economic evaluation is to provide an estimate of the cost-effectiveness of IPE in comparison with placebo. The economic evaluation also aims to identify important drivers of cost differences between the trial arms, the likely magnitude of cost differences and the likely magnitude of differences in health status to assist in the design of subsequent research and economic modelling in this area. The economic analysis will be conducted by the Academic Unit of Health Economics, University of Leeds, under the supervision of the lead Health Economist. The timeframe for the health economics analysis will be 4 months from receipt of the final dataset.

Health economic data will be collected at each trial visit using patient questionnaires and clinical records transcribed onto trial case report forms and by a Hospital Episode Statistics data download at the time of analysis. The scope will include secondary care costs, primary care and community NHS costs, patient out-of-pocket expenses and wider societal costs[57]. The calculation of Quality Adjusted Life Years (QALYs) will rely on the EuroQoL EQ-5D-5L questionnaire in order to weight survival for quality of life. The incremental cost effectiveness ratio will be calculated between trial arms. Outcomes will comprise: (i) cost per disease recurrence prevented at 2 years, and (ii) the cost per QALY at 2 years, both reported alongside the trial primary endpoint[57].

CRFs will, where possible, collect data in a manner consistent with activity types used by the NHS Reference Costs, from which unit costs will be assigned to secondary care activity. Other national sources of NHS unit costs such as the Commercial Medicines Unit Electronic Medicines Information Tool and the PSSRU Unit Costs of Health and Social care will be used to assign non-secondary care unit costs. A second analysis, performed as a sensitivity analysis, will use secondary care activity costed from linked Hospital Episode Statistics using the Department of Health HRG grouper software once this becomes available for 2 years follow-up for all patients

The non-parametric bootstrap method will be used to produce a within-trial probabilistic sensitivity analysis of the incremental cost effectiveness ratio. The impact of missing data will be examined using imputation methods. In addition to presenting the expected incremental cost effectiveness ratio, the scatterplot on the cost effectiveness plane the cost effectiveness acceptability curve and the expected value of perfect information will also be reported. The value based price of IPE will be calculated. Subgroup analysis will be conducted for trial stratification factors and any other factors described in the Statistical Analysis Plan.

17. Endpoints

17.1.1 Primary Endpoint

The primary endpoint is progression free survival (PFS) during a minimum of 2 years follow up. PFS is defined as the time from randomisation to death (from any cause), first documented evidence of disease progression (as defined in Section 13.11), new recurrence or clinical deterioration unequivocally due to disease progression[56]].

17.1.2 Secondary Endpoints

The secondary endpoints are:

- Overall Survival (OS), defined as the time from randomisation to death, from any cause (key secondary endpoint)
- Safety and tolerability of IPE before and after surgery, including during chemotherapy
- Patient reported quality of life, measured using the EQ-5D, EORTC QLQ-C30 and QLQ-LMC21 questionnaires
- Cost-effectiveness of IPE
- New primary cancers (excluding DCIS, cervical carcinoma *in situ*, superficial bladder carcinoma where treatment consisted of resection only and non-melanoma skin cancer where treatment consisted of resection or radiotherapy only)

17.1.3 Exploratory Endpoints

The exploratory endpoints are:

- Red blood cell membrane EPA content, measured at baseline, surgery and 6 months after surgery (only patients from Leeds and Sheffield)

- Change in lean body mass measured by CT scanning during follow up as assessed by the L3 skeletal muscle index score

18. Statistical Considerations

18.1 Sample size and planned recruitment rates

18.1.1 Sample size

A sample size of 448 participants (giving 247 events) is required to detect a HR of 0.7 for PFS in favour of EPA (the treatment arm) with a power of 80% at the 5% (2-sided) level of significance. This assumes the control arm has a median PFS of 21 months and the treatment arm has a median PFS of 30 months. It also assumes a 24 month recruitment period and a minimum 24 months follow up and allows for 10% dropout.

The HR for PFS in the Phase II EMT study[27] was 0.694, but the EPA arm, by chance, recruited a higher proportion of patients with poor prognostic features, and a multivariate analysis including these factors actually yielded a HR of 0.35 (95% confidence interval: 0.15-0.79) lending credence to the assumed more conservative HR of 0.7 chosen for this larger phase III study, given that the magnitude of benefit observed in phase II studies is often greater than that observed in the phase III counterpart.

The EMT study tested EPA-FFA 2g daily[27]. Although the EMT2 study will evaluate IPE 4 g daily, we assume similar efficacy of EPA given as IPE, compared with EPA-FFA, for the purposes of the trial power calculation.

The power calculation for the main secondary endpoint of OS uses a simulation approach based on an established mathematical model[58] that assumes a plateau in the time to event curves at around 4-5 years. Assuming 80% OS at 2 years in the control arm [28-29], and a difference between the treatment arms of 10% in the actuarial OS rate at 2 years (equivalent to a hazard ratio of 0.47 similar to that observed in the EMT study[27]), 448 patients (80 events) yields approximately 91% power to detect such a difference, and 78% power to detect a lesser HR of 0.55. This calculation again assumes 24 months recruitment and a minimum 24 months follow-up, a 5% (2-sided) significance level and a 10% dropout rate. Although this is an optimistic scenario, it is based on the EMT trial results[27], which suggested that it is entirely possible that EPA produces benefits both before and after progression, and this (secondary) endpoint encompasses that possibility. We note that OS is likely to be, if anything, slightly less than 80% at 2 years, from experience in the phase II EMT trial, which would increase the power under these assumptions.

In terms of the exploratory change in lean body mass endpoint, assuming a mean L3 skeletal muscle index score of the order of 50 cm^2/m^2, and a standard deviation of the order of 10 in

this score[59] then it would be possible to detect a relatively small mean difference between the treatment arms of 5 in the L3 skeletal muscle index (e.g. from 50 to 45) with 128 patients (64 in each arm) tested at the 12-month post-surgical follow-up with 80% power and using a 5% (2-sided) significance level. Therefore, this analysis is currently restricted to participants in Leeds and Sheffield. This high power with a small sample size is possible because we are looking at differences in a continuous variable, which yields higher sensitivity to changes on smaller numbers of patients.

18.1.2 Planned Recruitment Rate

We propose to recruit into this trial from eight sites incorporating the large UK hepatobiliary units offering 'high-volume' tertiary level CRCLM management. For a two-year recruitment period, the combined annual CRCLM resection rate of 890 patients (roughly 40% of the national workload) allows for a realistic 25% randomisation rate in order to recruit to time and target (224 per year). In the EMT study, only 4 of 203 (2%) CRCLM patients screened for eligibility refused to participate[27]. Although the excellent acceptability of the EMT study was aided by the dedicated study Research Fellow and single site-nature of the trial, we expect that the number of screened individuals who decline to participate will be low based on the preliminary data from the EMT study, combined with the excellent safety and tolerability profile of IPE. Given the relatively low number of exclusion criteria, we believe that a 25% recruitment rate allowing recruitment to time and target is realistic and obtainable despite the possibility of some placebo avoidance behaviour based on the phase II trial data[28].

19. Statistical Analysis

19.1 General Considerations

Statistical analysis is the responsibility of the CTRU Trial Statistician under the supervision of the Supervising Statistician, except for the health economic analysis which is the responsibility of the health economic TMG member. A full statistical analysis plan will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

19.2 Analysis populations

Analyses will be conducted on the intention to treat (ITT) basis where participants will be included according to which treatment they were randomised to receive, apart from the safety/tolerability endpoint which will be based on the safety population. The safety population

will consist of all patients who take at least one dose of any trial treatment; analyses based on the safety population will summarise participants according to treatment received. All hypothesis tests will be two-sided and will use a 5% significance level.

Sensitivity analyses may be performed for each endpoint, for example to take into account differing assumptions about missing data if there is a significant number of missing data, and will be detailed in the full statistical analysis plan.

19.3 Frequency of analysis

A DMEC will be set up to independently review data on safety and recruitment. Interim reports will be presented to the DMEC in strict confidence, on at least yearly intervals. This committee, in light of the interim data and of any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that one treatment is better. No formal interim analyses are planned hence no statistical testing will take place until final analysis.

We do not propose interim futility or early stopping (for superiority) analyses. Given the relatively short recruitment and follow-up periods in this trial, and the absence of a plausible reason to believe that outcomes would be worse in the EPA arm, we are highly unlikely to have observed sufficient events to stop for futility at 2½ years because of limited overall follow-up. Similarly, the relative paucity of events expected halfway through the four-year interventional period (i.e. at the end of recruitment) means that there would have to be a huge implausible difference in PFS in favour of EPA in order to stop for superiority.

The final analysis will take place after the last patient recruited has been followed up for 24 months.

19.4 Primary endpoint analysis

The primary endpoint is progression free survival (PFS) during a minimum of 2 years follow up (see section 17.1.1 for definition).

PFS will be analysed using the 95% confidence interval of the hazard ratio; the 95% confidence interval of the difference in median PFS will also be presented to aid interpretation. Kaplan-Meier survival curves will be calculated for PFS. Patients without a PFS event at the time of analysis will be censored at the time they were last known to be alive and progression-free. Differences in PFS between the treatment groups will be compared using multivariate modelling (for example, an extended Cox model if appropriate) to adjust for the minimisation factors of ‘downsizing’ chemotherapy, extrahepatic CRC metastases, randomising centre, and time between randomisation and surgery and also regular aspirin use during follow-up which will be included as a time dependent covariate. A sensitivity analysis will also be conducted to examine the effects of other potential effect modifiers in addition to the minimisation factors. The primary analysis will be the multivariate analysis which adjusts for the minimisation factors and regular aspirin use during follow-up. Treatment HRs and corresponding 95% confidence intervals will be obtained from the multivariate models.

19.5 Secondary endpoint analysis

Kaplan-Meier survival curves will be calculated for Overall Survival (OS). Participants without an OS event at the time of analysis will be censored at the time they were last known to be alive. Differences in OS between the treatment groups will be compared using multivariate modelling (for example, an extended Cox model if appropriate) to adjust for the minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate, and subsequent analyses will be conducted to examine the effects of other potential effect modifiers in addition to the minimisation factors. Treatment HRs and corresponding 95% confidence intervals will be obtained from the multivariate models.

Safety analyses will summarise the AE, AR, SAE, SAR and SUSAR rates per participant, by treatment received and overall. Suspected relationship to IPE will be presented along with other causality, outcome and event duration.

QoL will be measured using the general EQ-5D and cancer specific EORTC QLQ-C30 and QLQ-LMC21 questionnaires. These will be analysed using random effects (multi-level) models to account for the hierarchical nature of repeated measures data and the models will include adjustments for baseline QoL, the minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate, with subsequent sensitivity analyses to adjust for any other potential effect modifiers in addition to the minimisation factors. The nature of any missing data will be investigated and if it is suspected that data are not missing at random alternative analyses will be carried out to allow for the nature of the missing data.

The number and timing of new primary cancers will be summarised descriptively by treatment group.

19.6 Subgroup Analyses

A subgroup analysis comparing the outcomes for patients that receive ≥2 weeks of IMP prior surgery and patients that receive <2 weeks of EPA will be performed. Further subgroup analyses will be performed to investigate the effect of aspirin and EPA and the effect of EPA on the MSI status of the primary colorectal cancer on PFS.

19.7 Exploratory endpoint analysis

Red blood cell membrane EPA content will be measured at baseline, at surgery and 6 months after surgery in all participants from Leeds and Sheffield[52]. The effect of red blood cell membrane EPA content on disease-related outcomes (PFS and OS) will be analysed using an extended Cox model (if appropriate) which will adjust for the minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate and will also include red blood cell membrane EPA content as a time dependent covariate. Subsequent sensitivity analyses will be conducted to adjust for any other potential effect modifiers in addition to the minimisation factors.

Lean body mass will be measured longitudinally from the routine CT abdomen images using the method of Baracos (based on muscle area at the L3 vertebral level)[44]. The difference in muscle mass between the EPA and placebo treatment groups will be analysed using a random effects (multi-level) model to account for the hierarchical nature of the repeated measures data. The model will be adjusted for the baseline muscle mass, minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate, with a subsequent sensitivity analysis to adjust for any other potential effect modifiers in addition to the minimisation factors. A possible association between changes in muscle mass and disease related outcomes (PFS and OS) will be analysed using an extended Cox model (if appropriate) which will adjust for the minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate, and will also include lean body mass as a time dependent covariate. A subsequent sensitivity analysis will be carried out to adjust for any other potential effect modifiers as well as the minimisation factors.

Weight will also be analysed as a measure of cachexia. The difference in weight of patients between the treatment arms will be analysed using a random effects (multi-level) model to account for the hierarchical nature of the repeated measures data and will be adjusted for baseline weight, the minimisation factors and regular aspirin use during follow-up, which will be included as a time dependent covariate. A sensitivity analysis will also be carried out to adjust for other potential effect modifiers as well as the minimisation factors.

Analysis of the biospecimens collected during the sub-study 'The prebiotic effect of EPA treatment for CRCLM' are detailed in Appendix A of the Biospecimen Collection protocol. Laboratory work will take place in Leeds Institute of Medical Research and ICT, University of Bradford, as well as Massachusetts General Hospital and Harvard School of Public Health in Boston, USA.

20. Trial Monitoring

20.1 Data Monitoring and Ethics Committee (DMEC)

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and Trial Steering Committee (TSC) based on the trial risk assessment; this may include on site monitoring.

The independent DMEC will review the safety and ethics of the study. Detailed unblinded reports will be prepared by the CTRU for the DMEC at approximately 6 monthly intervals. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan.

Any unblinded interim reports provided to the DMEC will be provided by the CTRU Safety Statistician for consideration in a closed session and the reports will be securely password-protected.

20.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. However, missing data items will not be chased from participants (although missing questionnaires sometimes are). The CTRU will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

20.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

21. Quality Assurance, Ethical and Regulatory Considerations

21.1 Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF), and through adherence to CTRU Standard Operating Procedures (SOPs).

21.2 Serious Breaches

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined by Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A “serious breach” is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial; or

b) the scientific value of the trial

For further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

21.3 Ethical considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996. Informed written consent will be obtained from the participants prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The trial will be submitted to and approved by a main REC and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the trial. The CTRU will provide the main REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

22. Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth and hospital ID
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.

- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.

- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment or from further collection of data, their data and samples will remain on file and will be included in the final trial analysis.

The trial staff at the participating sites will be responsible for ensuring that any data / documentation sent to the CTRU is appropriately anonymised as per instructions given by CTRU in accordance with the trial procedures to conform with the 1998 Data Protection Act.

23. Archiving

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Sponsor archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

24. Statement of indemnity

The University of Leeds will be liable for negligent harm caused to participants treated in the UK that is caused by the design of the study.

The NHS has a duty of care to patients treated in the UK, whether or not the patient is taking part in a clinical study, and the NHS remains liable for harm to UK patients due to clinical negligence under this duty of care.

25. Study Organisational Structure

25.1 Individuals and Individual Organisations

Chief Investigator (CI) – The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and NHS Permissions submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

Academic Unit of Health Economics, University of Leeds – The Academic Unit of Health Economics will conduct the economic analysis, under the supervision of the lead Health Economist.

Central pharmacy – Stockport Pharmaceuticals, Stepping Hill Hospital, Poplar Grove, Stockport. The central pharmacy is responsible for the labelling, packaging and distribution of trial IMP.

Central laboratory - Institute of Cancer Therapeutics, University of Bradford. The central laboratory is responsible for the red blood cell fatty acid analysis.

25.2 Oversight and Trial Monitoring Groups

Trial Management Group (TMG) – The TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial and a nursing representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC) – The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members

and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up and will report to the TSC. The Committee will meet annually as a minimum.

26. Publication Policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee and Yorkshire Cancer Research. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

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Appendix A: Schedule of Events

Events		Standard practice surgery eligibility checks	**Visit 1** (0 months)	2 weekly telephone calls******	**Visit 2: Surgery** (<6 weeks post randomisation)	**Visit 3** (6 months)*	**Visit 4** (12 months)	**Visit 5** (18 months)	**Visit 6** (24 months)	**Visit 7** (30 months)	**Visit 8** (36 months)	**Visit 9** (42 months)	**Visit 10**/Exit Visit (48 months)	60days post treatment end (phone call)
Clinical Procedures/ Assessments	CT thorax/abdomen/pelvis	x			**	x	x	x	x		x		x	
	Weight		x		x	x	x	x	x	x	x	x	x	
	Blood sample***		x		x	x								
	CRCLM surgery				x									
	AE assessment			x	x	x	x	x	x	x	x	x	x	x
	Concomitant medications		x	x	x	x	x	x	x	x	x	x	x	
	Pregnancy test****		x											
	Compliance monitoring			x	x	x	x	x	x	x	x	x	x	
	Biospecimen collection (optional)*****		x		X******	x		x		x			x	
Trial interventions	Randomisation		x											
	IMP dispensing		x		x	x	x	x	x	x	x	x		
Participant Completed Questionnaires	Participant Questionnaire Visit 1 Pack		x											
	Participant Questionnaire Visit 2 Pack				x									
	Participant Questionnaire Visit 3-10 Pack					x	x	x	x	x	x	x	x	
Data Collection through CRFs			x	x	x	x	x	x	x	x	x	x	x	x

*For Visit 3 and subsequent trial assessments, there is the possibility of remote (telephone) follow up in which case body weight is self-reported, blood sampling is not required and IMP is sent via courier to the participant's postal address.

**In the event that macroscopic disease remains following liver resection and curative treatment is not possible, a CT scan should be carried out as soon as possible to measure the extent of the existing disease.

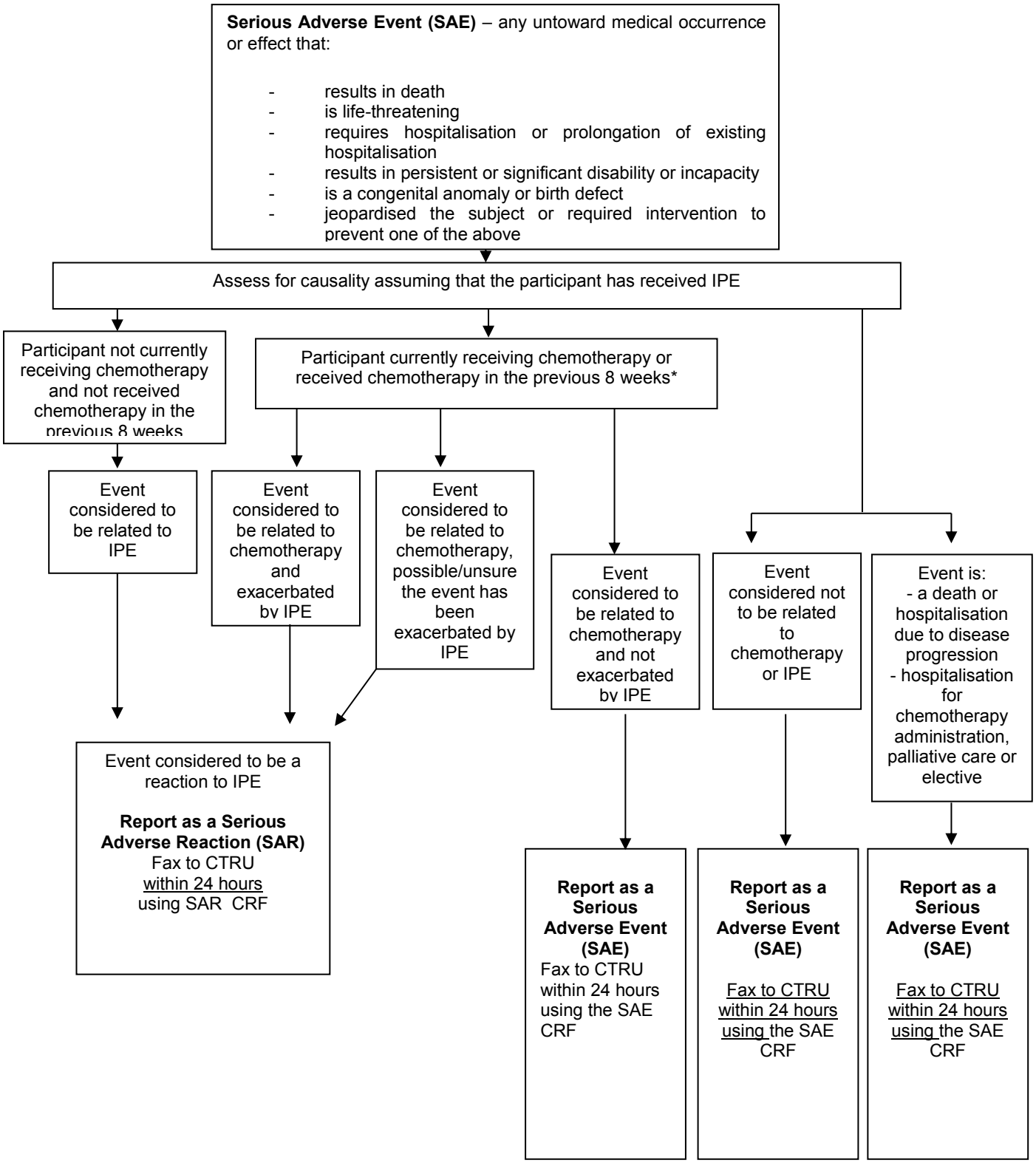
*** Blood sample collection at Sheffield Teaching Hospitals NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust.

**** For women of child bearing potential: following consent, the participant must be registered before the pregnancy test is performed as this is a trial specific test. The participant cannot be randomised until a negative test has been obtained.

***** See separate Biospecimen Collection protocol.

****** Only if CRCLM surgery is ≥2 weeks from randomisation.

Appendix B: Pharmacovigilance Reporting Flowchart



Appendix C: Safety Monitoring Plan

Study Title: **EMT2**

Risks associated with trial interventions

☐ LOW ≡ Comparable to the risk of standard medical care

☒ MODERATE ≡ Somewhat higher than the risk of standard medical care

☐ HIGH ≡ Markedly higher than the risk of standard medical care

Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):*

This trial involves the use of familiar drugs in line with standard practice.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
IPE	Upper and lower gastrointestinal symptoms	Recommend that the capsules are taken with food.	Twice daily	Dose reduction algorithm (section 12.2.4) to be used in the event that symptoms do not resolve. This includes the option for a temporary treatment break during chemotherapy.

A data monitoring and ethics committee (DMEC) will be convened who will periodically (at least annually) review unblinded safety information. The DMEC will in light of these reports, have the authority to recommend trial closure to the Trial Steering Committee (TSC) should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend closure of the trial to the sponsor at any time.

Participant data will be entered onto a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. A validation check program will be incorporated into the database to verify the data, and discrepancy reports will be generated for resolution by the local investigator. Priority validations will be incorporated into the validation program to ensure that any discrepancies related to participant rights or the safety of participants are expedited to participating centres for resolution.

Appendix D: Response Evaluation Criteria in Solid Tumours (RECIST)

In the case of macroscopic disease (liver and extra-hepatic metastases) remaining following surgical resection response to treatment will be assessed based on RECIST v1.1[56]. A copy of the revised RECIST guideline is provided in the Investigator Site File and may also be obtained at:

http://www.eortc.be/recist/

Published date: January 2009[56].