TACE-2

A randomised placebo-controlled, double blinded, phase III trial of sorafenib in combination with transarterial chemoembolisation in hepatocellular cancer

UCL

UNIVERSITY OF BIRMINGHAM

NCRN National Cancer Research Network

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AUTHORISED BY

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Role Chief Investigator	**Date 14/9/16**
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Role Sponsor's Representative	**Date**

GENERAL INFORMATION

Protocol

This document was developed by the Trial Management Group with the approval of the UK NCRI Upper GI Clinical Study Group's hepatobiliary subgroup. This document describes the "TACE-2" trial. Every care has been taken in drafting this document, but corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but centres entering patients for the first time are advised to contact the TACE-2 Trials Office to confirm they have the most up-to-date version.

This protocol has been written in accordance to the sponsor's procedure outlined in the SOP identified as: JBRU/INV/S01/00

Sponsor

University College London (UCL)
Named Sponsor' Representative: **Nick McNally** (Director of Research Services)
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Funding

This international study is a clinician-initiated and clinician-led study supported by the NIHR and funded by educational grants from Bayer and Biocompatibles UK. UCL will be the overall sponsor for this trial. Sorafenib and matching placebo will be supplied at no cost by Bayer and free DC Bead® will be supplied by Biocompatibles UK.

Compliance

This trial will adhere to the principles outlined in the Good Clinical Practice (GCP) guidelines. It will be conducted in compliance with the protocol, Data Protection Act 1998 and other regulatory requirements, as appropriate.

Authorisation

The following persons are authorised to sign the final protocol and protocol amendments for the Sponsor: Dr Tim Meyer (Chief Investigator) and Sponsor's representative: Nick McNally (Director of Research Services)

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This trial has been developed by the Trial Management Group.

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CLINICAL QUERIES

Clinical queries during office hours should be directed to the trials office

Protocol Synopsis

Short Title TACE-2

A randomised placebo-controlled, double-blinded, phase III trial evaluating sorafenib in combination with transarterial chemoembolisation (TACE) in patients with unresectable hepatocellular carcinoma (HCC)

Design

Prospective, Phase III, International, Multicentre, Two Arm, Randomised, Double-Blinded, Clinical Trial

Trial Objectives

To determine whether the addition of sorafenib to TACE (performed according to a standardised protocol with doxorubicin eluting beads) is superior to TACE alone in the treatment of HCC

Sample Size

The trial aims to recruit 206 patients in each arm (412 patients in total)

Trial Duration

It is anticipated that recruitment will take approximately three years and the study will continue for a further year after the last patient has been recruited. Estimated start date for recruitment is November 2010 and will end by first quarter 2015. All patients will be followed up for one year after the last administration of sorafenib/placebo and will be flagged with the Medical Research Information Service until death.

Outcome Measures

Primary: Progression Free Survival

Secondary: Overall Survival; Time to Progression; Toxicity; Disease Control (CR+PR+SD); QoL and number of TACE procedures performed during 12 months following randomisation

Eligibility Criteria

Inclusion Criteria

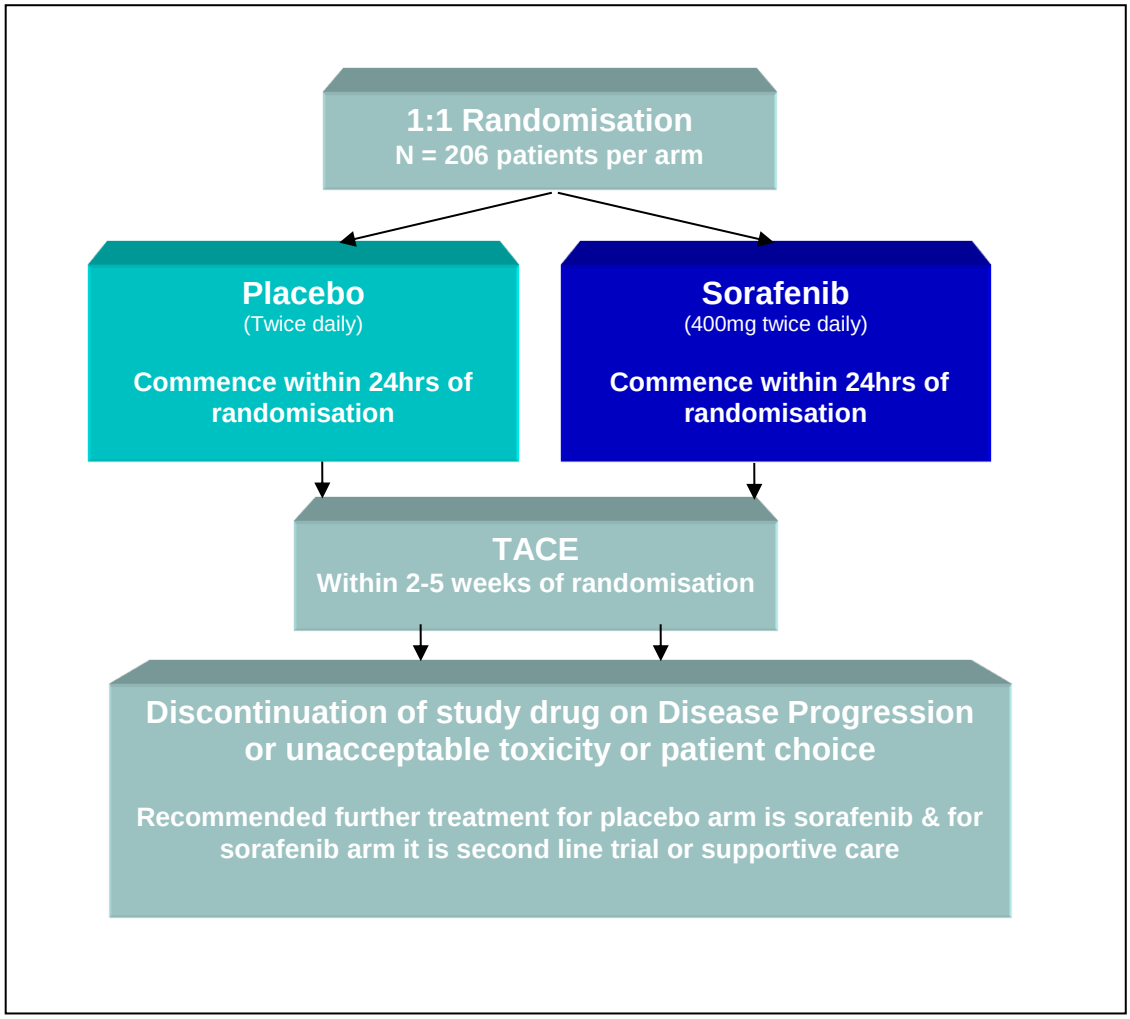
- Histological or cytological diagnosis or meet the AASLD criteria (Appendix 1) for diagnosis of HCC and at least one uni-dimensional lesion measurable according to the RECIST criteria by CT-scan or MRI (Appendix 2)
- Not a candidate for surgical resection or liver transplant
- Aged ≥18 years and estimated life expectancy >3 months
- ECOG performance status ≤1 (Appendix 3)
- Adequate haematological function Hb ≥9g/L, absolute neutrophil count ≥1.5x10^9/L, platelet count ≥60x10^9/L
- Bilirubin ≤50 µmol/L, AST or ALT ≤5 x ULN, ALP <4 x ULN
- Adequate renal function; Creatinine ≤1.5 x ULN
- INR ≤1.5
- Amylase <2 x ULN
- Child-Pugh cirrhosis A (score must be ≤6) (Appendix 4)
- Left Ventricular Ejection fraction ≥45%
- Women of child-bearing potential should have a negative pregnancy test prior to study entry. Both men and women must be using an adequate contraception method, which must be continued for 3 months after completion of treatment
- Written informed consent

Exclusion Criteria

- Extrahepatic metastasis
- Prior embolisation, systemic or radiation therapy for HCC
- Any contraindications for hepatic embolisation procedures including portosystemic shunt, hepatofugal blood flow, known severe atheromatosis
- Investigational therapy or major surgery within 4 weeks of trial entry
- Any ablative therapy (RFA or PEI) for HCC (this should not exclude patients if target lesion(s) have not been treated and occurred >6 weeks prior to study entry)
- History of bleeding within the past 4 weeks
- Child-Pugh cirrhosis C and B with score ≥7 (Appendix 4)
- Hepatic encephalopathy
- Ascites refractory to diuretic therapy
- Documented occlusion of the hepatic artery or main portal vein
- Hypersensitivity to intravenous contrast agents
- Active clinically serious infection > grade 2 NCI-CTC version 4 (Appendix 5)
- Pregnant or lactating women
- Known history of HIV infection

- History of second malignancy except those treated with curative intent more than three years previously without relapse and non-melanotic skin cancer or cervical carcinoma in situ
- Evidence of severe or uncontrolled systemic diseases, cardiac arrhythmias (requiring anti-arrhythmic therapy or pace maker), uncontrolled hypertension, congestive cardiac failure >NYHA class 2 (Appendix 6), MI within 6 months, prolonged QT/QTc >450ms, or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial
- Psychiatric or other disorder likely to impact on informed consent
- Patient is unable and/or unwilling to comply with treatment and study instructions
- Patient is unable to swallow oral medications

Trial Schema



LIST OF ABBREVIATIONS

Abbreviation	Explanation
AASLD	American Association for Study of Liver Disease
AE	Adverse Event
AR	Adverse Reaction
BCLC	Barcelona Clinic Liver Cancer
CRF	Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
HCC	Hepatocellular Cancer
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MTD	Maximum Tolerated Dose
PD	Progressive Disease
PFS	Progression Free Survival
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised Controlled Trial
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TACE	Transarterial Chemoembolisation
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Time To Progression
UAR	Unexpected Adverse Reaction

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1 BACKGROUND AND RATIONALE

1.1 Background

Primary liver cancer is the sixth most common cancer worldwide, with over 600,000 new cases a year and it is the third most common cause of cancer death [1, 2]. Mortality from this cancer has roughly trebled in the last 25 years in the UK [3] and is increasing in the USA and the rest of Europe [4, 5, 6, 7]. The numbers are expected to continue to increase over the next two decades due to the hepatitis C epidemic ([2,8,9]). Less than 30% of patients with hepatocellular cancer (HCC) are suitable for potentially curative therapies such as resection or transplantation and of these up to 50% will ultimately relapse and die from their disease [10]. There is therefore an urgent need to develop a more effective therapy for unresectable HCC.

1.2 Trans-arterial Chemoembolisation

Two randomised controlled trials have shown that trans-arterial chemoembolisation (TACE) performed with doxorubicin or cisplatin improves survival in selected patients with HCC compared to best supportive care [11, 12]. A subsequent meta-analysis including 7 trials and 545 patients reported a 2-year overall survival rate in treated patients of 41% (range, 19%-63%) versus 27% (range, 11%-50%) in the control group (odds ratio, 0.53; 95% confidence interval, 0.32-0.89; P =0.017) [10,11, 12]. Such benefit has not been demonstrated for trans-arterial embolisation (TAE) alone. On this basis TACE became the recommended first line non-curative therapy for non-surgical/multifocal HCC by the 2006 American Association for the Study of Liver Diseases (AASLD) guidelines [13]. In spite of the proven efficacy of TACE, treatment is associated with toxicity and mortality. Post embolisation syndrome consisting of pain, nausea and fever occurs in 60-80% of patients but is self-limiting lasting for 3-4 days. Less common but more serious side effects include liver failure 7.5%, ascites 8.3%, gastrointestinal bleeding 3%, liver abscess 1.3%, renal failure 1.8% and bile duct injury 2% [14]. Treatment related 30-day mortality has been reported in 0-9.5% of patients treated with a median rate of 2.4%. Appropriate patient selection reduces the risk of serious side effects as demonstrated in the two positive RCTs [11, 12].

- **TACE using Drug Eluting Beads**

There is heterogeneity in the practice of TACE with respect to embolic particle, use of lipiodol, type of chemotherapy and frequency of administration and there is currently no widely accepted standard technique [14]. A recent innovation is the drug eluting bead (DC Bead®, Biocompatibles UK) that allows well-controlled embolisation with the delivery of a high local dose of chemotherapy and low systemic exposure. DC Bead® are based on a polyvinyl alcohol (PVA) that has been modified with sulfonate groups and can be loaded

with doxorubicin. In pre-clinical models, systemic exposure to doxorubicin was 70-80% lower in animals treated with DC Bead® compared to those receiving intra-arterial doxorubicin. Within the tumour, doxorubicin peaked at 3 days and remained high for 7 days before declining at 14 days [15]. Three phase I and II trials including a total of 124 patients have so far been published evaluating the efficacy and toxicity of this intervention in HCC [16, 17, 18].

1) Varela *et al.,* (2007) [16]: Twenty-seven Child-Pugh A patients with large or multifocal HCC were treated with DC Bead® (diameter range 500-700µm) loaded with escalating doses of doxorubicin (47-150mg). Two sessions were given at 2-month intervals. The response rate was 66% by EASL criteria and 44% by RECIST and 1 and 2 year survival rates were 92 and 89% respectively. By comparison with conventional TACE performed with gelfoam and lipiodol, the C_{max} and AUC for doxorubicin were significantly lower with DC Bead®. Post embolisation syndrome occurred in 37% of patients and liver abscess occurred in two patients, one of whom died.

2) Poon *et al.,* 2007 [17]: Fifteen patients were treated in the phase I dose escalation part of this study using a dose range of 25-150mg doxorubicin. Twenty patients went on to receive 150mg doxorubicin in the phase II component. All were Child-Pugh class A. Treatment was repeated at 2 months with response assessment in 30 patients performed one month after the second TACE. By RECIST the response rate was 50% and by EASL criteria 70%. The treatment related complication rate was 11.4% and there were no treatment related deaths.

3) Malagari *et al.,* 2008 [18]: In this phase II trial, 62 patients with a single lesion with a mean diameter of 5.6cm were included. Fifty-three were Okuda stage 1 and nine were stage 2. Planned treatment was with 4mls DC Bead® ranging from 100-500µm loaded with 150mg doxorubicin repeated on three occasions at 3-monthly intervals. Following the first procedure 60% had achieved an objective response by EASL criteria. All patients experienced some degree of post embolisation syndrome. One patient developed a liver abscess and one developed cholecystitis. There was no procedure related mortality.

In summary DC Bead® appear to be an effective and safe method of performing TACE. Response rates with DC Bead® appear to be at least as good as with conventional TACE and they are associated with a reduced systemic exposure of doxorubicin. The toxicity profile is acceptable with an overall mortality rate of 1% amongst the 124 patients included in the published trials. As the control arm of a TACE trial, DC Bead® are therefore an attractive technique, which allows standardisation of approach across all centres.

1.3 Sorafenib in Hepatocellular Cancer

Sorafenib is an orally active multikinase inhibitor that blocks both tumour cell proliferation by targeting the RAF/MEK/ERK signalling pathway, and angiogenesis by inhibition of VEGF-R2, VEGF-R3 and PDGF-β. Phase I trials have defined the maximum tolerated dose at 400mg bd with dose limiting toxicities being diarrhoea, fatigue and hand foot syndrome [19, 20]. Other drug related adverse reactions included anorexia.

Sorafenib was assessed in a large multinational phase II trial of 137 patients with advanced HCC and Child-Pugh A (72%) or B (28%) cirrhosis [21]. Patients were treated with 400mg bd continuously and were assessed every 8 weeks. The response rate was 2.2% and 33.6% had stable disease over 16 weeks. Median time to progression was 4.2 months and median overall survival was 9.2 months. Grade 3/4 drug-related toxicities included fatigue (9.5%), diarrhoea (8.0%), and hand foot reaction (5.1%). There were no significant differences in pharmacokinetic parameters between Child-Pugh A and B patients.

In 2008, the results of the multinational SHARP trial were reported [22] in which 602 patients with advanced HCC were randomly allocated to sorafenib 400mg bd or matched placebo. At baseline 96% were Child-Pugh class A, 82% were BCLC stage C, 92% had ECOG performance status 0/1 and 70% had either macroscopic portal vein involvement or extrahepatic spread. The objective response rate was 2.3% in the treatment group and 0.7% in the placebo group while progression free survival at 4 months was 62% and 42% respectively. Median time to progression was 5.5 months on sorafenib and 2.8 months on placebo and there was a 44% (HR=0.69; p-value < 0.001) improvement in median overall survival from 7.9 to 10.7 months [22,23]. Grade 3/4 adverse events were consistent with the phase II trial with 8% experiencing diarrhoea and hand foot skin reaction and 32% required a dose reduction. Notably less than 1% had grade 3/4 bleeding in both groups. More recently, a second placebo controlled, randomised trial performed in an Asian population has confirmed the relative survival benefit in sorafenib treated patients [24].

Until the presentation of the SHARP trial, no systemic therapy had ever been shown to improve survival in HCC over best supportive care and on this basis sorafenib is now widely regarded as the standard of care for BCLC stage C patients and should be used as the control arm of subsequent phase III trials in this subgroup.

- **Sorafenib and doxorubicin in combination**

Doxorubicin has been widely used for the treatment of HCC despite a lack of clear evidence that it prolongs life. The combination of doxorubicin with sorafenib has been explored in a phase I trial in which 34 patients, with a variety of solid tumours, received

doxorubicin at 60mg/m^2 with escalating doses of sorafenib up to 400mg bd [25]. The MTD was not reached and drug related adverse events included neutropenia, hand foot skin reaction, stomatitis and diarrhoea. With sorafenib (400mg bd), the exposure to doxorubicin was moderately increased but, within the limitations of this small study, no additional clinical consequences could be identified. Similar results have been reported in a series of 18 patients with HCC [26].

More recently the results have been presented [27] of a randomised phase II trial comparing single agent doxorubicin with doxorubicin plus sorafenib in 96 patients with advanced HCC. At baseline, patients were all Child-Pugh class A, over 90% had ECOG PS 0-1 and just over half in each group had extrahepatic disease. There was no difference in serious adverse events nor 30 day mortality between the two groups and a pre-planned exploratory analysis of overall survival demonstrated a median of 6.5 months for doxorubicin compared with 13.7 months for the combination arm (HR 0.45, p=0.0049). Since the efficacy of doxorubicin remains unproven, it is currently unclear whether a synergy exists between the two drugs and this will require formal testing in a trial comparing sorafenib alone with the combination. However, it is clear that the two drugs can be safely combined at full doses in patients with advanced HCC.

1.4 Study Rationale

TACE trials have included 80% BCLC B stage (intermediate) patients with disease confined to the liver, good performance status and no main portal vein invasion. By contrast, sorafenib has been tested in a subgroup of patients in which 82% were BCLC stage C (advanced) and would not have been considered suitable for TACE because of portal vein invasion, extrahepatic disease or poor performance status.

A key question now is whether the outlook for intermediate stage disease can be improved by concurrent treatment with TACE and sorafenib. Sorafenib is a small molecule inhibitor of the VEGF pathway and RAF/MEK/ERK cascade [28, 29]. There is a clear rationale for combining TACE with sorafenib as VEGF is important in angiogenesis and levels increase following embolisation [30, 31]. These higher serum levels are linked to tumour metastasis and reduced survival of patients after TACE [32, 33,34]. In addition, the RAF/MEK/ERK cascade plays a role in the development of HCC [35, 36, 37]. Therefore sorafenib, which inhibits both these pathways, is an exciting candidate for combination with TACE. There are other new targeted-agents such as bevacizumab and sunitinib, which have shown promise in Phase II HCC studies. These have yet to demonstrate a survival advantage in a Phase III setting making sorafenib the first choice for combination with TACE. We therefore propose a randomised, placebo controlled trial in which patients will receive sorafenib or placebo immediately on randomisation, TACE performed within 2-5 weeks

following randomisation and sorafenib/placebo continued until progression. TACE will be standardised by using DC Bead® loaded with doxorubicin according to a common protocol. The studies discussed above demonstrate that doxorubicin and sorafenib can be safely combined and there is a potential synergy that requires further evaluation. On progression, patients on placebo will be offered sorafenib. The primary endpoint will be progression free survival (PFS) with secondary endpoints being overall survival, time to progression, toxicity and quality of life. The addition of sorafenib as an adjuvant to TACE may reduce the rate of tumour regrowth and increase the interval for repeat TACE.

2 AIMS, OBJECTIVES AND OUTCOME MEASURES

- **The primary objective**

The primary objective is to determine whether the addition of sorafenib to TACE, performed with doxorubicin eluting beads (DC Bead®, Biocompatibles), prolongs progression free survival in patients with HCC compared to TACE alone.

- **The secondary objectives**

The secondary objectives are to determine whether the addition of sorafenib to TACE performed with doxorubicin eluting beads (DC Bead®, Biocompatibles):-

- prolongs overall survival
- prolongs time to progression
- has acceptable toxicity
- affects disease response (CR & PR & SD)
- affects Quality of Life (QoL)
- reduces the frequency for repeat TACE as measured by number of TACE procedures performed in 12 months following randomisation

- **Translational sub-studies**

A blood sample bank linked to this study will be established for biomarker research (proteomic and genomic analysis). Patients will be invited to provide additional blood samples for research. A TACE-2 Translational Study Patient Information Sheet will be provided and patients will indicate their consent on the TACE-2 Translational Study consent from. Refusal to consent to this additional blood collection will not exclude the patient's participation in the therapeutic trial. Blood will be collected at screening,

randomisation, within 24 hours before 1st TACE, 24 hours after 1st TACE and at week 10 and 22 post randomisation. A standard operating procedure will be provided. Patients will also be invited to provide consent for research to be performed on residual tumour or liver tissue that has been taken for diagnostic purposes. Separate protocols will be written for each sub-study that will use the samples provided and ethical approval will be sought from the appropriate ethics committee. Following the closure of the trial no further blood samples will be sought from patients. Any existing samples retained at sites shall be sent to the blood sample bank.

3 TRIAL DESIGN

3.1 Overall Study Design

This is a Phase III multicentre, randomised, double-blind, placebo-controlled study. The trial aims to recruit 206 patients in each arm (412 patients in total). Patients will be recruited from major liver centres in the UK and Ireland.

Patients with intermediate stage HCC who fulfil the eligibility criteria will be randomly assigned, on a 1:1 basis, to sorafenib or matching placebo in combination with TACE in a double-blinded fashion.

Sorafenib (or matching placebo) at 400mg bd will commence within 24 hours of randomisation and will continue until disease progression (as defined in Section 13).
TACE will be performed between 2 and 5 weeks after randomisation using DC Bead® (see see section 7) and may be performed as per local NHS standard practice thereafter, if preferred over the use of DC Bead®.

3.2 Progression Notification

Sites are required to inform the Trials Unit in Birmingham of locally identified progression at the earliest opportunity (ideally within 7 days of the date of the scan) by faxing the Progression Notification Form to the Trials Unit. This form must be signed by an Investigator.
The corresponding Disease Assessment Form is to be completed as soon as possible, and entered onto the TACE-2 database or returned to the TACE-2 Trial Office.

On progression patients on the placebo arm will be offered sorafenib at the discretion of the treating clinician and will be considered as having 'crossed over' and will be followed up for survival. Patients on the sorafenib arm would normally discontinue but may be offered further sorafenib. All patients will be followed-up for a further year after the last

administration of the blinded sorafenib/placebo treatment and will be flagged with the Medical Research Information Service until death.

Once the patient has progressed, the patient will continue to be followed up according to protocol.

The primary outcome measure is progression free survival with secondary measures being overall survival, time to progression, toxicity, disease response, QoL, number of repeat TACE procedures and translational measures.

3.3 Blinding and Ongoing Trial Treatment

Patients will be randomised to receive sorafenib or matching placebo in a double-blind fashion such that neither the Investigator, nor the patient will know which combination is being administered. Following the trial's closure to recruitment, all patients will be notified of their treatment allocation. Patients on blinded sorafenib treatment prior to closure, who in consultation with their medical team, may continue to receive further supplies of sorafenib as deemed necessary and where the withdrawal of the treatment would be detrimental to that patients ongoing care. Patients on blinded placebo treatment may remain on trial following the trial's closure to recruitment and receive TACE procedures only. Patients who remain on trial will be re-consented to the trial following the trial's closure to recruitment.

Study medication will be labelled with a unique number (Treatment Pack Number) which will be assigned to a patient.

3.4 Trial Duration

It is anticipated that recruitment will take approximately 4years and the study will continue for a further year after the last patient has been recruited. It is estimated that recruitment will start November 2010 and be complete by the first quarter of 2015.

3.5 Trial Treatment Period

The start of the study treatment period is the date of randomisation. The end of the study treatment period is the date of disease progression (see section 3.2) or discontinuation of study drug due to unacceptable toxicity or patient choice or death. All Serious Adverse Events should be reported from the start of study treatment until 30 days after last administration of blinded therapy.

3.6 Post study-treatment period

On progression (see section 3.2), patients will discontinue active study treatment and those on placebo can receive sorafenib treatment at the discretion of the treating clinician The post-study period is defined as that between the discontinuation of study treatment and the end of the follow up period.

3.7 Long Term Follow-up

On completion of the recruitment period, all patients will be followed up for a further year after the last administration of blinded sorafenib/placebo and will be flagged with the Medical Research Information Service until death.

3.8 Source Data

Source data is all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial. In the following cases the CRF will be considered the source document: Patient Diaries and Quality of Life booklets.

4 ELIGIBILITY AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

- Histological or cytological diagnosis or meet the AASLD criteria (Appendix 1) for diagnosis of HCC and at least one uni-dimensional lesion measurable according to the RECIST criteria by CT-scan or MRI (Appendix 2).
- Not a candidate for surgical resection or liver transplant
- Aged ≥18 years and estimated life expectancy >3 months
- ECOG performance status ≤1 (Appendix 3)
- Adequate haematological function Hb ≥9g/L, absolute neutrophil count ≥1.5x10^9/L, platelet count ≥60x10^9/L
- Bilirubin ≤50 µmol/L, AST and ALT ≤5 x ULN, ALP <4 x ULN
- Adequate renal function; Creatinine ≤1.5 x ULN
- INR ≤1.5
- Amylase <2 x ULN
- Child-Pugh A (score ≤6) (Appendix 4)
- Left Ventricular Ejection Fraction ≥45%
- Women of child-bearing potential should have a negative pregnancy test prior to study entry. Both men and women must be using an adequate contraception method, which must be continued for 3 months after completion of treatment
- Written informed consent

4.2 Exclusion Criteria

- Extrahepatic metastasis
- Prior embolisation, systemic or radiation therapy for HCC
- Any contraindications for hepatic embolisation procedures including portosystemic shunt, hepatofugal blood flow, known severe atheromatosis
- Investigational therapy or major surgery within 4 weeks of trial entry
- Any ablative therapy (RFA or PEI) for HCC (this should not exclude patients if target lesion(s) have not been treated and occurred >6 weeks prior study entry)
- History of bleeding within the past 4 weeks
- Child-Pugh cirrhosis C or B (score ≥7)
- Hepatic encephalopathy
- Ascites refractory to diuretic therapy
- Documented occlusion of the hepatic artery or main portal vein
- Hypersensitivity to intravenous contrast agents
- Active clinically serious infection > Grade 2 NCI-CTC version 4 (Appendix 5)
- Pregnant or lactating women
- Known history of HIV infection
- History of second malignancy except those treated with curative intent more than three years preciously without relapse and non-melanotic skin cancer or cervical carcinoma in situ
- Evidence of severe or uncontrolled systemic diseases, cardiac arrhythmias (requiring anti-arrhythmic therapy or pace maker), uncontrolled hypertension, congestive cardiac failure >NYHA class 2 (see Appendix 6), MI within 6 months, prolonged QT/QTc >450ms, or laboratory finding that in the view of the Investigator makes it undesirable for the patient to participate in the trial
- Psychiatric or other disorder likely to impact on informed consent
- Patient is unable and/or unwilling to comply with treatment and study instructions
- Patient unable to swallow oral medications

4.3 Withdrawal from Trial

Withdrawal from the trial is only applicable for

- Patient withdrawal of consent
- Patient Death

In the event of a patient's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the appropriate CRF. All patients will continue to be followed by Medical

Research Information Service, and all information and blood/tissue samples collected up until point of retraction will be retained and analysed.

If a patient chooses to withdraw from treatment only, the patient should discontinue treatment and continue to be assessed in accordance with the protocol and where appropriate radiological scans as per local standard of care.

If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the Trials Office, then further routine "follow-up" data (e.g. progression status, survival, TACE procedures, further treatment) will continue to be supplied by the Investigator to the Trials Office.

If a patient wishes to withdraw from an Ancillary Study e.g. QoL study or Translational Study, the patient should continue in the main trial, but no more QoL data, blood or tissue will be gathered for that particular study from the date of retraction.

5 PATIENT SCREENING AND CONSENT

Prior to recruitment of patients into the study the Principal Investigator or designee should have returned all required documentation to the Trials Office and site personnel involved with TACE-2 and must have received appropriate training from the Trial Coordinator.

5.1 Patient Screening

Potential patients will be identified via clinic referrals or the Multi-disciplinary Team meeting.

Investigators will be expected to maintain a Screening Log of all potential study candidates. This Log will include limited information about the potential candidate (e.g. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

For patients who appear to meet the criteria for participation in the study, the Investigator will provide information to allow them to make an informed decision regarding their participation. If informed consent is given, the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. A patient who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be randomised into the study. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated number of weeks prior to randomisation (see Section 8 Pre-randomisation evaluations).

5.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to trial entry and prior to performing assessments that are not conducted as standard of care. A Patient Information Sheet is provided to facilitate this process. Trial information is also on the National Cancer Research Network website: http://public.ukcrn.org.uk/search. Further information will also be available on the trial website: www.tace-2.bham.ac.uk

Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (at least 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the Research Team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial, they should be asked to sign and date the latest version of the Consent Form in the presence of the Investigator who must then co-sign and date the form. The patient must personally initial all boxes. A copy of the Consent Form should be given to the patient, a copy should be filed in the hospital notes and the original should be placed in the Investigator Site File (ISF). In addition, if the patient has given explicit consent, a copy should be sent in the post to the trials office for review. Once the patient is entered into the trial, the patient's trial number should be entered on the Consent Form maintained in the ISF. A dated annotation should be made in the patient's medical notes stating consent has been given, with the name of the trial and the version number of the Patient Information Sheet and Consent Form. Details of patients randomised into the trial should be recorded on the Patient Enrolment Log.

Electronic copies of the Patient Information Sheet and Consent Form are available from the TACE-2 Trial Coordinator and should be printed or photocopied onto the headed paper of the local institution. With their prior consent, the patient's General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose. Throughout the study, the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner.

6 TRIAL ENTRY

Patients will be randomly assigned, on a 1:1 basis and in a blinded fashion, to the sorafenib or placebo arm. To accomplish this, randomisation will be based on a minimisation randomisation algorithm. Randomisation will be stratified by (i) randomising centre and (ii) serum alpha-fetoprotein levels (<331, ≥331 kU/L (<400, ≥400 ng/ml)).

An eligibility checklist and randomisation form should be completed prior to randomisation by the Investigator or designee. These details can be phoned or faxed through to the **TACE-2 Trials Office** at the CRCTU, Birmingham.

Online: https://www.cancertrials.bham.ac.uk/TACE2

☎: **0800 371 969; 9am-5pm GMT Monday to Friday**

Non-UK centres: +44 121 414 3366

Fax: 0800 328 6412

Treatment will be allocated after checking eligibility and recording baseline patient details. The allocated trial number and treatment pack number will be given via the online system or over the telephone and confirmed by fax.

A treatment pack will contain 70 days supply of sorafenib/matching placebo. New treatment packs will be dispensed from local pharmacy as required (usually at 6 weekly follow-up).

7 TREATMENT DETAILS

For the purposes of the trial, sorafenib and matching placebo are both classed as Investigational Medicinal Products (IMP). TACE is a background treatment and as such is classed as a Non Investigational Medicinal Product (NIMP).

7.1 Treatment Supplies

- **Sorafenib and matching placebo**

Sorafenib will be supplied as 200 mg tablets. Both IMPs will be provided free of charge for the duration of the study by Bayer. Full pharmacy details and guidelines for ordering study drug supplies, storage, labelling requirements and codebreak procedure will be supplied within the TACE-2 Pharmacy File and further information can be found in the Summary of Product Characteristics. Sharp Clinical Services UK Limited, Elvicta Business Park, Crickhowell, Powys, NP8 1DF, will be responsible for the labelling and distribution of trial drug to sites.

- **Doxorubicin**

Doxorubicin is not subsidised for the purpose of this study and will be sourced from routine hospital stock. The handling and management will be subject to standard procedures of the pharmacy. 50 mg vials of Doxorubicin-HCl powder should be used with DC Bead®. NOTE only Doxorubicin-HCl is suitable for DC Bead® loading. Liposomal formulations of doxorubicin are not suitable for loading into DC Bead®. Further information on Doxorubicin can be found in the Summary of Product Characteristics. Instructions for loading Doxorubicin-HCl into DC Bead® is detailed in Appendix 7 of the protocol.

TACE

- **DC Bead®**

DC Bead® is a CE marked drug delivery embolisation system and is indicated for the treatment of malignant hypervascularised tumours and loading with doxorubicin. The DC Bead® nominal size range to be used in this study is between 100-300μm and 300-500μm. In a minority of cases 500-700μm beads may be used. DC Bead® will be provided free of charge for the study by Biocompatibles UK Ltd, Chapman House, Farnham Business Park, Weydon Lane, Farnham, Surrey, GU9 8QL. Full pharmacy details and guidelines for ordering device will be supplied within the TACE-2 Pharmacy File. Instructions for loading Doxorubicin-HCl into DC Bead® is detailed in Appendix 7 of the protocol.

Following the trial's closure to recruitment TACE can also be performed in line with local NHS standard practice and the choice of beads will be trust supplies.

7.2 Planned Interventions

- **Sorafenib or matching placebo**

Patients should take two 200mg sorafenib tablets or matching placebo orally twice daily until progression or discontinuation due to toxicity or patient choice.

- **TACE**

The first TACE will be performed between 2 and 5 weeks after randomisation using DC Bead® loaded with Doxorubicin-HCl 150mg (see Appendix 7 for further information on loading).

An assessment dual phase CT or enhanced MRI scan will be performed at baseline, week 10 and week 22 after randomisation and according to local standard of care thereafter. In the absence of complete devascularisation of the tumour(s), as assessed by follow-up contrast enhanced scan, further TACE should be performed unless technical or patient factors preclude retreatment. Subsequent TACE procedures and the indication for these must be recorded on the appropriate CRF. All TACE procedures undertaken prior to trial closure should be performed with DC Bead® and according to local NHS standard practice thereafter. After six procedures further TACE with DC Beads® should only be performed if the left ventricular ejection fraction is ≥45% on repeat assessment. If the ejection fraction is <45% bland embolisation with unloaded DC Bead® should be performed. For TACE procedures using local NHS standard practice, local procedures for further administration and management of TACE should be followed.

See section 7.6 for advice on permitted further treatment with TACE once a patient is withdrawn from study treatment (i.e. sorafenib or placebo). If there are new lesions or progression of existing lesions, the progression endpoint will have been met and the patient must be unblinded. Patients may discontinue study treatment. NOTE In the event of progression (according to RECIST) further treatment with TACE or sorafenib may be appropriate at the discretion of the local Investigator.

7.3 Dose Modifications

Study medication will be continued until the criterion for stopping is reached. In response to toxicities described below, the dose will be reduced to predefined levels:

Full dose:	400mg bd (twice daily)
Level -1:	400mg qd (once daily)
Level -2:	400mg qod (alternate days)

- **Hand Foot Syndrome**

Definition of Grade

Grade 1	Minimal skin changes or dermatitis (e.g. erythema, edema or hyperkeratosis) without pain
Grade 2	Skin changes (e.g. peeling, blisters, bleeding, edema or hyperkeratosis) with pain; limiting instrumental ADL
Grade 3	Severe skin changes (e.g. peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL

Grade		Action	On Resolution to Grade 0-1
Grade 1		Continue full dose	Continue full dose
Grade 2	1st appearance	Discontinue until resolved to grade 0-1	Continue full dose
	2nd appearance	Discontinue until resolved to grade 0-1	Reduce to dose level -1
	3rd appearance	Discontinue until resolved to grade 0-1	Reduce to dose level -2
	4th appearance	Discontinue	Discontinue permanently
Grade 3	1st appearance	Discontinue until resolved to grade 0-1	Reduce to dose level -1
	2nd appearance	Discontinue until resolved to grade 0-1	Reduce to dose level -2
	3rd appearance	Discontinue	Discontinue permanently

- **Haematological Toxicity**

Definition of Grade - see NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4)

Grade	Action
Grade 0-2	Continue treatment at full dose
Grade 3	Reduce dose by one level and continue treatment[a]
Grade 4	Discontinue treatment until resolved to grade 0-2 and restart at reduced level[b]

[a] if no recovery to grade 0-2 within 30 days reduce level again. If no recovery to grade 0-2 within a further 30 days, or dose already reduced, discontinue study treatment

[b] if no recovery after 30 days discontinue study treatment

- **Non-Haematological Toxicity**

Definition of Grade - see NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4)

Grade	Action
Grade 0-2	Continue treatment at full dose
Grade 3	Discontinue treatment until resolved to grade 0-2 and restart at reduced level[a]
Grade 4	Discontinue treatment

[a] if no recovery after 30 days discontinue study treatment

- **Management of Treatment-Emergent Hypertension**

Blood pressure will be measured at every clinic visit and blood pressure monitoring by local GP is recommended

Grade	Action
Grade 1 asymptomatic and transient	Consider increased BP monitoring
Grade 2 asymptomatic and diastolic BP < 110 mm Hg	Begin anti-hypertensive therapy and continue sorafenib

Grade 2 symptomatic/persistent OR Diastolic BP ≥110 mm Hg OR **Grade 3**	Discontinue treatment[a] until symptoms resolve and diastolic BP returns to ≤100 mm Hg. Treat subject with anti-hypertensives and restart at reduced level[b] If diastolic BP not controlled to ≤100 mm Hg on therapy, reduce treatment by another dose level and monitor BP closely[c]
Grade 4 life-threatening	Discontinue treatment

- **Monitoring of ECG Readings**

ECGs will be carried out according to the schedule in Appendix 12. Sorafenib should be discontinued if QT/QTc increases over 500ms or increases to 60ms above the baseline reading.

Please note that specific criteria are not completely identical to NCI-CTCAE V4 criteria
[a] Subjects requiring a delay of >28 days should discontinue treatment
[b] May be able to resume full dose later
[c] Subjects requiring >2 dose reductions should discontinue treatment

7.4 Concomitant Medication

This refers to all non-study treatment/medication received by the patient during the study from date of randomisation up until 30 days after last administration of blinded therapy.

Permissible concomitant medication/therapies:

- Treatment with non-conventional therapies (for example: herbs or acupuncture), and vitamin/mineral supplements is acceptable, provided that in the opinion of the investigator, they do not interfere with the study endpoints
- Patients may receive palliative and supportive care for any underlying illness
- Best Supportive Care which may include analgesics and other non-antineoplastics
- Medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator

Non-Permissible concomitant medication/therapies:

- Rifampicin and St John's Wort
- Investigational therapy
- Bone marrow transplant or stem cell rescue
- Bevacizumab and any drugs that target VEGF or VEGF receptors

- Anti-cancer chemotherapy, immunotherapy, hormone therapy or molecular therapy except bisphosphonates

Patients taking narrow therapeutic index medications should be monitored proactively. These include Warfarin, Phenytoin, Quinidine, Carbamazepine, Phenobarbital, Cyclosporin and Digoxin.

7.5 Withdrawal from Study Treatment

In the event of discontinuation of study treatment, full details of the reason/s for discontinuation should be recorded on the appropriate pages on the CRF. All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent (see section 4).

A patient should discontinue study drug (i.e. sorafenib or placebo) in the event of any of the following:

- Disease Progression according to RECIST criteria
- Unacceptable toxicity
- Any other adverse event which, in the Investigator's opinion, requires termination of the study medication
- Administration of radiotherapy, an investigational agent or any anti-tumour therapy other than study TACE during the trial
- Pregnancy
- Any other reason given by the Investigator
- The patient uses illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results
- The development of a second malignancy that requires treatment
- Request by the patient or a legal representative/relative to stop the treatment
- Death or End of Study

7.6 Permitted Further Treatment

Further treatment is at the discretion of the clinician. Further TACE is permitted if clinically indicated. However, in the absence of evidence, concomitant treatment with sorafenib during repeat TACE is not recommended.

When a patient progresses (see Section 3.2), patients previously receiving placebo will be treated according to local standard of care and may be offered sorafenib if the treating physician feels the patient will derive clinical benefit. Patients on the sorafenib arm would normally discontinue but may be offered further sorafenib where clinically indicated.

Sorafenib will be supplied from clinical trial stock without charge to the sponsor for the remainder of the long term follow up period. Further sorafenib supplies can be sought from local practice through the Cancer Drugs Fund.

7.7 Drug Accountability & Drug Destruction

The trial pharmacist will be responsible for maintaining and updating the drug accountability log in the TACE-2 pharmacy file. All unfinished bottles will be returned to the trial pharmacist who will count and document any unused medication. All Investigational Medicinal Products can then be destroyed in accordance with local pharmacy practice and this will be documented on the drug destruction log in the hospital pharmacy file.

To monitor compliance, patients will be issued with a Patient Diary (Appendix 13) at the start of each treatment cycle. Patients will be asked to complete the diary, recording the time that each dose was taken, and whether any doses were missed. The diary also includes a section where the patient can record any relevant information such as side effects suffered or reasons for missed doses. The completed diary will be collected by the centre at clinic visits and returned to the TACE-2 Study Office.

8 STUDY ASSESSMENTS

See Appendix 12 for Flowchart of Assessments

8.1 Pre-Randomisation

The following procedures will be performed within 4 weeks prior to randomisation

- Informed consent
- Confirmation of diagnosis of HCC according to AASLD guidelines or histology
- Medical history
- Physical examination including vital signs and weight
- ECOG performance status
- Concomitant drug history
- Full blood count and clotting (PT, INR) and Serum biochemistry
- Alpha fetoprotein
- Hepatitis B and C antigen and antibody

- ECG
- LVEF determined by either MUGA scan or echocardiogram
- Chest CT and dual phase CT or contrast enhanced MRI scan of abdomen
- Documentation of Child-Pugh score
- Pregnancy test in women of child bearing potential
- Collection of Biomarker blood

8.2 Randomisation

The following will be performed on the day of randomisation

- Physical examination including vital signs, blood pressure and weight
- ECOG performance status
- Concomitant drug history
- Full blood count and clotting (PT, INR) and Serum biochemistry
- Alpha fetoprotein
- Documentation of Child-Pugh score
- QoL assessment
- Collection of Biomarker blood
- Arrangements for TACE to be performed within 2-5 weeks from randomisation. In the case of extensive bilobar disease in which a single session treatment could lead to liver decompensation, treat only one lobe. The second lobe should be treated ideally within 2-3 weeks and both treatments completed within 6 weeks of randomisation
- Commence study drug – sorafenib or placebo
- Issue patient diary

8.3 2-5 weeks post-randomisation

The following should be performed within 72 hours pre-1st TACE

- Toxicity assessment
- Physical examination including vital signs, blood pressure and weight
- ECOG performance status
- Concomitant drug history
- Full blood count and clotting (PT, INR) and Serum biochemistry
- Alpha fetoprotein
- Documentation of Child-Pugh score

- ECG
- QoL assessment
- Collection of Biomarker blood
- Review and collect patient diary

TACE should be performed with DC Bead® according to manufacturer's instructions. See Appendix 7

8.4 24 hours post-1st TACE

- Biomarker Bloods

8.5 1 week post-TACE

If necessary, blood tests can be performed locally and assessment of ECOG performance assessed by telephone

- Toxicity assessment
- ECOG performance status
- Full blood count and clotting (PT, INR) and Serum biochemistry
- Documentation of Child-Pugh score
- ECG
- Blood pressure

8.6 Week 10 (post-randomisation)

- Radiological assessment of response using same modality as baseline
    - If progressive disease is identified at radiological review, ensure the Trials Unit are informed immediately using the Progression Notification Form (see section 3.2).
- If there is residual tumour vascularity further TACE should be performed before week 15. Prior to subsequent TACE, the patient should have adequate haematological, renal and liver function as per inclusion criteria.
- Toxicity assessment
- Physical examination including vital signs, Blood pressure, weight
- ECOG performance status
- Concomitant drug history
- Full blood count and clotting (PT, INR) and serum biochemistry
- Alpha feto-protein
- Documentation of Child-Pugh score

- ECG
- QoL assessment
- Review and collect patient diary

8.7 Week 16 (post-randomisation) and every 6 weeks until progression

- Toxicity assessment
- Physical examination including vital signs, Blood pressure, weight
- Concomitant drug history
- ECOG performance status
- Full blood count and clotting (PT, INR) and serum biochemistry
- Alpha feto-protein
- Documentation of Child-Pugh score
- ECG
- QoL assessment
- Review and collect patient diary
- Radiological assessment of response as per standard of care.
    - If progressive disease is identified at radiological review, ensure the Trials Unit are informed immediately using the Progression Notification Form (see section 3.2).

8.8 Week 22 (post-randomisation)

The following will be done **in addition** to the 6 weekly assessments described above

- Radiological assessment of response using same modality as baseline
    - If progressive disease is identified at radiological review, ensure the Trials Unit are informed immediately using the Progression Notification Form (see section 3.2).
- Document decision about further TACE to be performed. Prior to subsequent TACE, the trial entry criteria should be met. Scans may be done more frequently if clinically indicated

8.9 Week 34 (post-randomisation) and 12 weekly thereafter until progression

The following will be done **in addition** to the 6 weekly assessments described above

- Document decision about further TACE to be performed. Prior to subsequent TACE, the trial entry criteria should be met.

9 SAFETY ASSESSMENTS

9.1 Definition of Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical trial patient administered study treatment (i.e. TACE or sorafenib or matching placebo) and which does not necessarily have a causal relationship with the treatment received.

Comment: *An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of the study treatment, whether or not it is considered related to the study treatment.*

9.2 Definition of Adverse Reaction

An Adverse Reaction (AR) is defined as all untoward and unintended responses to study treatment related to any dose administered.

Comment: *An AE judged by either the reporting Investigator or Sponsor as being possibly related, probably related, or definitely related to study therapy will qualify as an AR.*

9.3 Definition of Unexpected Adverse Reaction

An Unexpected Adverse Reaction (UAR) is defined as an AR, the nature or severity of which is not consistent with the applicable product information.

Comment: *When the outcome of an AR is not consistent with the applicable product information, the AR should be considered unexpected.*

If the Investigator suspects that the disease has progressed faster due to the administration of the IMP, then they will report this as an unexpected adverse event to the Trials office.

9.4 Definition of Serious Adverse Event

An SAE is defined as any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator (i.e. an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above)

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an unplanned, overnight, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE

Comment: The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

9.5 Definition of Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is a SAE judged by either the reporting Investigator or Sponsor as being possibly related, probably related, or definitely related to study therapy.

9.6 Definition of Suspected Unexpected SAR (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAR that is unexpected i.e. the nature, seriousness, severity (i.e. grade) or outcome of the event is not consistent with the applicable product information.

9.7 List of Expected Adverse Reactions

For a list of all expected adverse reactions please refer to the Summary of Product Characteristics (SmPC) for sorafenib and for the TACE procedure, refer to both the related SmPC for doxorubicin and the list of AEs for the embolisation procedure given in Appendix 11.

9.8 Assessment of Adverse Events

For all AEs, the Investigator will determine the grade (i.e. severity), seriousness and causality (i.e. relationship to study therapy) as described below. When assessing SAEs the Investigator must assume that the patient received the active IMP (i.e. sorafenib).

- **Grade (i.e. severity)**

All events should be graded according to the NCI CTCAE Toxicity Criteria (Version 4)

For events not listed in the toxicity table, severity should be recorded as:

Mild	**Does not interfere with patient's usual functioning**
Moderate	Interferes to some extent with patient's usual functioning
Severe	Interferes significantly with patient's usual functioning

Life threatening	Risk of death, organ damage or disability

- **Causality (i.e. Relationship to Study therapy)**

Relationship to study therapy will be assessed using the following definitions:

Unrelated	**There is no evidence of any causal relationship**
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Possibly related	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

9.9 Independent Assessment of Causality and Expectedness

Seriousness and causality of all reported SAEs will be determined independently by the TACE-2 Clinical Coordinator. An SAE judged by the Chief Investigator, or delegated Clinical Coordinator, to have a reasonable causal relationship with the trial medication will be regarded as a SAR (i.e. possibly related, probably related, or definitely related to study therapy). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected in nature it will be classified as a SUSAR.

10 SAFETY REPORTING

10.1 Adverse Event Reporting

Investigators should give details of all AEs and SAEs from date of first study treatment until 30 days after the last exposure to blinded therapy. SUSARs related to the

Investigational Medicinal Product (IMP) will need to be reported to the sponsor irrespective of how long after IMP administration the reaction occurred.

Patients should be followed up until resolution of the event. All AEs should be recorded on the appropriate page of the CRF, including date of onset, grade, seriousness, duration and relationship to study therapy and outcome.

Collection, recording and notification of AEs (including serious and non serious events and reactions) to the sponsor by the trials office will be done according to the sponsor's SOP and the agreement between both parties.

10.2 Expedited Serious Adverse Event Reporting

Investigators or their designee should report all SAEs in an expedited manner (i.e. within 24 hours of becoming aware of the event) according to the following procedure.

- Complete an SAE Form (If more than one SAE occurs, each event will be recorded separately on a new form) and a fax cover sheet
- The SAE Form can be completed and signed by a member of the site trial team delegated this responsibility by the Investigator, but should be checked and counter signed by the Investigator at a later date
- Fax the SAE Form to the Trials Office. Ensure that a return fax is received back from the Trials Office, confirming receipt
- Adhere to any local institutional policy relating to SAE reporting
- Continue to follow the patient up until clinical recovery is complete or any sequelae has stabilised
- Provide follow-up information on an SAE Form on resolution of the event

NOTE: when assessing SAEs the Investigator must assume that the patient received sorafenib

The Trials office will report to the sponsor all SAEs & SARs in accordance with the sponsor's SOP and the agreement between both parties.

10.3 SAEs that do not require Expedited Reporting

Hospitalisation for the purpose of the TACE treatment, and lasting for up to 7 days after that treatment, does not require reporting unless associated with other serious events. Hospitalisation lasting for >7 days post TACE OR re-admissions within 7 days (i.e. if the patient is discharged from hospital and then returns within 7 days), require reporting in the usual manner as outlined above.

Although not reported as a serious adverse event, details of length of stay in hospital will be captured on the relevant page of the CRF.

10.4 Notification of deaths

All deaths will be reported to trials office irrespective of whether the death is related to disease progression, the Investigational Medicinal Product, or an unrelated event within 24 hours. The Trials Office will notify the sponsor of SAE related deaths within 7 days.

10.5 Notification of Pregnancy

As there is no data on the use of sorafenib in pregnant women or in animal studies, sorafenib is anticipated to cause harmful effects on the foetus as well as indicating impairment to male and female fertility. Therefore, sorafenib should not be used during pregnancy. Women of childbearing potential will require a negative serum pregnancy test prior to randomisation and must agree to use 2 forms of effective contraception during treatment and for some time after stopping treatment.

All pregnancies/suspected pregnancies occurring during the study treatment period or within 30 days after the last exposure to sorafenib/matching placebo must be recorded on the Notification of Pregnancy Form and faxed to the trial office within 24 hours of the research staff becoming aware of the event. The Chief Investigator will review it accordingly and decide whether it should be forwarded onto the MHRA.

Patients will be unblinded and their study medication discontinued immediately. The patient will be instructed to return any unused study medication to the investigator.

Female patients should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

The pregnancy should then be followed up by the investigator to determine outcome, including spontaneous or voluntary termination, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

If the father is the trial participant, informed consent to report information regarding pregnancy outcome needs to be obtained from the mother

10.6 Codebreaks

Following the closure to recruitment all patients will be notified of their treatment allocation and no further codebreaks will be necessary in the event of a serious adverse event being deemed unexpected and possibly, probably or definitely related to the IMP and classified as a SUSAR by the Investigator or TACE-2 Clinical Co-ordinator.

10.7 Reporting by Sponsor

All unexpected serious adverse reactions will be notified to the sponsor immediately according to the sponsor's SOP. Reporting by the Sponsor or Sponsor's delegated representative is in line with the "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use April 2006".

For the purposes of the trial sorafenib and matching placebo are both classed as Investigational Medicinal Products (IMP), whilst TACE is classed as background treatment and a Non Investigational Medicinal Product (NIMP).

- **SUSAR reporting in Member State concerned**

The Sponsor, or delegated representative, shall report all individual events which are unexpected and suspected to be related to sorafenib, or matching placebo, or to be linked to an interaction between sorafenib, or matching placebo, and TACE, to the Competent Authority and the Ethics Committee in the Member State concerned as follows:-
If a SUSAR is categorised as a fatal or life threatening SUSAR, a minimal data set of all individual events will be sent within 7 days with detailed follow-up information provided within an additional 8 days.
All other events categorised as SUSARs will be reported within 15 days to the Competent Authority and the Ethics Committee in the concerned Member State.

- **Regular SUSAR reports to Ethics Committees in other Member states**

All SUSARs from other Member States will be periodically reported at least every 6 months as a line listing accompanied by a brief report by the Sponsor/Trials Office highlighting the main points of concern. Those periodic reports shall only include SUSARs reported within the period covered by the report.

- **Development Safety Update Report (DSUR)**

In addition to the above, the sponsor or delegated sponsor's representative shall submit, once a year throughout the clinical trial or on request, a safety report to the Competent Authority and the Ethics Committee of all concerned Member States, taking into account all new available safety information received during the reporting period. The DSUR will

describe concisely all new safety information relevant for this trial and it will assess the safety of subjects included in this study. Details of all SUSARs and any other safety issue which arise during the course of the trial will be compiled into a report, and sent to all Investigators by a TACE-2 trial representative. The frequency of reporting will be dependent on the volume of SUSARs generated and the significance of the safety issue but it will be at least every 6 months. The line listing will present data on all SUSARs, regardless of the medication administered (e.g. active/placebo), thereby when possible and appropriate, the blind is maintained and the risk of inadvertently informing the investigators with regard to the identity of the medication is avoided.

- **Other Safety Issues Identified During the Course of the Trial**

The Trials Office/Sponsor shall notify the Competent Authority and the Ethics Committee in all the concerned Member States immediately if a significant safety issue is identified during the course of the trial.

- **Bayer/Biocompatibles UK**

Safety reporting to Bayer or Biocompatibles by the sponsor or delegated sponsor's representative will be in accordance with the signed agreement between both parties.

11 QUALITY OF LIFE

QoL is an important outcome measure and as such all patients will be invited to participate in the QoL study. Patients who consent will be assessed using validated instruments developed by the EORTC QoL Group: the EORTC QoL questionnaire (QLQ-C30) version 3 and EORTC QLQ-HCC18 a site-specific module for HCC. The EORTC questionnaires will assess both general and hepatocellular specific aspects of quality of life. Patients will also be asked to complete a EuroQoL (EQ-5D) questionnaire which will enable the patient's current health state to be valued for use in calculating quality-adjusted life years (QALYs). These will be collated into a QoL booklet which will be given to patients to complete prior to treatment with the reasons for any non-compliance recorded. QoL booklets will be coordinated with routine clinic visits and requested at baseline, pre TACE, week 10 and 6-weekly thereafter until progression.

The EORTC QLQ-HCC18 site-specific module for HCC has completed phases 1 to 3 of questionnaire development, and has been approved by the EORTC module development committee and currently submitted for publication.

12 DEFINITION OF OUTCOME MEASURES

12.1 Progression Free Survival (PFS)

PFS is defined as the interval between the date of randomisation and the date of progression or death from any cause. Progression will be defined by RECIST criteria (see Appendix 2 for more detail) compared against the baseline pre-randomisation CT or MRI. The imaging modality used to define progression must be the same as that used at baseline. . Surviving patients without progression will be censored at date last seen.

12.2 Overall Survival

Overall survival time is the time between the date of randomisation and death from any cause. Patients discontinuing the study, lost to follow-up or still alive at the end of the study will be censored at the last known date alive.

12.3 Time to Progression (TTP)

TTP is defined as the interval between the date of randomisation and the date of progression. Progression will be defined by RECIST criteria compared against the baseline pre-randomisation CT or MRI. The imaging modality used to define progression must be the same as that used at baseline. Patients who have not progressed by the end of the study will be censored at date last seen. Patients who have not progressed and have died will be censored at their date of death.

12.4 Toxicity

Adverse events and serious adverse events will be graded according to the revised NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4) from start of study treatment up to 30 days after last administration of study treatment or until end of study.

12.5 Disease Control [CR+PR+SD] and progression [PD]

Response will be assessed using the RECIST guidelines. Response according to modified RECIST criteria will also be recorded separately but only PD by RECIST will trigger unblinding. The scan done prior to randomisation will be considered the baseline scan and the same modality must be used for all follow-up assessments. PD will be externally validated. Unblinding will occur upon local diagnosis of PD confirmed by receipt at the Trials Unit of a Progression Notification Form, signed by the PI. (See also section 3.2)

12.6 Quality of Life (QoL)

QoL will be assessed using the EORTC QoL questionnaire (QLQ-C30) version 3, EORTC QLQ-HCC18, a site-specific module for HCC and the EuroQoL (EQ-5D) questionnaire

requested at baseline, pre TACE, week 10 and 6-weekly thereafter until progression. QoL will be scored according to the EORTC QLQ-C30 manual and guidelines.

13 STATISTICAL CONSIDERATIONS

13.1 Power Calculations

A feasibility questionnaire was sent out to all centres that had expressed interest to obtain an estimate of recruitment. 15 UK sites returned the questionnaires as well as 6 sites from both France and Italy.

As it was estimated that the French and Italian sites would not open until years 2 and 3 respectively, the estimated recruitment was calculated as follows:

	UK	France	Italy	Total estimate
Estimated annual recruitment	218	112	170	
Year 1	50%	0%	0%	109
Year 2	100%	50%	0%	273
Year 3	100%	100%	50%	415
			Total for 3 years / 2	399

The total estimate for recruitment from interested sites was divided by two to provide a cautious estimate of 399 patients over 3 years.

The primary research question to be addressed is to compare efficacy in terms of progression-free survival (PFS) of TACE plus sorafenib and TACE plus placebo in patients with hepatocellular cancer. Current evidence is that TACE has shown a 35% 12-month PFS rate and median PFS of 8.9 months (TACE-1, personal communication). The SHARP trial has shown a 3-month increase in median Time To Progression (TTP) using Sorafenib from 12.3 to 24 weeks (HR=0.69) and improvement in median overall survival from 7.9 to 10.7 months.

Power calculations are based on one-year and median PFS rates and expectant Hazard Ratio (HR). Confirmation of the planned recruitment sites has allowed power calculations to be based on a 36 month accrual period and 12 month follow up period of all patients. The one-year PFS on the TACE plus placebo arm is assumed to range between 30-40% and the proposed trial will be powered to detect a clinically meaningful absolute increase in PFS of 12% with sorafenib. This equates to the detection of 3.5 month increase in median PFS from 8.9-12.4 months and an estimated HR $_{TACE+S}$ of 0.72, translated assuming exponential survival. Calculations assume a log-rank test will be carried out with a two-

tailed 5% significance level. Recruiting 206 patients in each treatment arm over a 36 month period, with additional follow-up of 12-months following the recruitment period, will allow these survival differences to be detected using a 2-sided level of significance of α=0.05 with 85% power. If the true median survival times are 8.9 and 12.4 months for TACE with placebo and sorafenib respectively, the null hypothesis that the survival distributions are equal can be rejected with 85% power. Numbers of patients are estimated using PS software (version 3.0.2) developed by Dupont and Plummer at Vanderbilt University and which is available free from their website. The software is based on methods described by Schoenfeld and Richter in Biometrics 1982.

Machin and Campbell sample size software (version 2.5) calculate that the study will require at least 340 events to achieve 85% power, as above.

The assumptions behind these sample size calculations will be re-examined periodically by an independent data monitoring committee during the course of the trial, and modified as appropriate.

The number of patients lost to follow-up for the primary outcome measure is expected to be minimal (existing studies report $\leq$6%) but will obviously be monitored rigorously. The Data Monitoring Committee (DMC) may advise recruitment of additional patients based on the number of patients lost to follow up if numbers are higher than anticipated. The number of patients who do not comply with the protocol is expected to be low. All protocol violators will be reported but will be included in the final analysis within their randomised group on an intention-to-treat basis.

13.2 Analyses of Outcome Measures

All analyses will be carried out on an intention to treat basis, retaining patients in their randomised treatment groups and including protocol violator and ineligible patients, in order to maintain the unbiased comparison of treatments created by the randomisation procedure. A sensitivity analysis excluding ineligible patients may be conducted and reported. Analyses will be according to the detailed Statistical Analysis Plan (SAP) for the Trial using the statistical software packages Stata, SAS and R. The SAP is version controlled and any amendments to the plan will be documented.

The primary aim is to test the null hypothesis of no difference between the two treatment arms in terms of PFS. Disease status is assessed under the RECIST criteria. The primary analysis will consider the local disease assessment only. A sensitivity analysis based on the results of the central review of disease status may be performed. Survival estimates (progression-free, overall and time to progression) will be calculated using the method of Kaplan and Meier, and the Mantel-Haenszel version of the log-rank test will be used to assess differences in survival estimates across treatment groups and across important patient characteristic or histological groups. Any treatment effect will be adjusted by

stratification factors and other identified prognostic factors using stratified log-rank analyses and in a multivariate setting using Cox proportional hazards and/or random effects modelling. Hazard ratios of the treatment effect (without significance testing) within identified prognostic subgroups will be estimated and presented graphically with tests of heterogeneity. Analyses of overall survival may be confounded since patients can cross-over to the active arm upon disease progression. These analyses are sensitive to the assumption of proportional hazards and, as such, methods that adjust for this confounding will be considered once the assumption can be assessed.

Toxicity will be graded according to the NCI CTCAE v4 criteria and the proportions of grade 3/4 toxicity will be reported descriptively across treatments. Additional treatment required during or after protocol treatment will be recorded and presented descriptively across treatment groups.

Objective Disease Response will be determined according to the RECIST criteria and patients will be grouped for comparison across treatments according to their 'best' response. Response rates are calculated by dividing the total number of patients with CR or PR (on 'best' response) by the total number of patients randomised per treatment group. The proportions of patients achieving a response will be compared descriptively with 95% CI and compared across treatments using Pearson's chi-square test.

Quality of life will be analysed using longitudinal statistical methods comparing treatment group with appropriate consideration given to missing data due to dropout and death. Questionnaire responses will be combined and transformed into dimension scores and the mean change from baseline score compared using the Mann-Whitney test. Standardised area under the curve analysis will be used to assess mean observed symptomatic and functional QoL over a complete period of 12 months from randomisation whilst minimising multiple testing. Global QoL scores and utility scores form the EQ-5D will be assessed in a quality-adjusted survival analysis to enable simultaneous assessment of QoL and survival, to account for drop-out due to death and censored QoL estimates (from patients remaining alive). Quality adjusted survival analysis within 12 months of randomisation using the integrated quality-survival product method will be used.

The number of additional TACE procedures will be recorded in each arm and reported descriptively with medians and ranges.

13.3 Planned subgroup analyses

Hazard ratios of the treatment effect (without significance testing) within identified prognostic subgroups, including stratification factors, will be estimated and presented graphically with tests of heterogeneity.

13.4 Planned Interim Analyses

Reports for the DMC will be produced by the trial statistician. A first report will be prepared based on the first 30 patients recruited into each treatment group or when the study has been open to recruitment for at least 12 months, whichever is the sooner. This aim of this initial report is to assess recruitment, compliance to treatment, toxicity (including reported serious adverse events) and 30-day mortality rates, specifically in relation to the combination of sorafenib with TACE.

Thereafter the DMC will meet annually, or more often if requested by the DMC, to monitor recruitment and toxicity (including reported serious adverse events) as well as assessment of primary and secondary outcome measures including response rates and survival. The DMC will be requested to consider the trial data accounting for other current worldwide evidence as well as review and make recommendations regarding the continuation of the study and the validation of the underlying assumptions for the sample size.

The trial may be stopped or amended by the Trial Steering Committee if proof beyond reasonable doubt emerges that one or other treatment is clearly indicated or contra-indicated as considered by the DMC in light of the interim analyses. In terms of efficacy, the DMC would have to be in no doubt that there should be a change to clinical practice and would have to feel that it was unethical to continue to randomise. Regarding safety, the DMC would have to be in no doubt that safety was a major concern and would have to feel that it was unethical to continue to randomise. If any change to the trial is recommended, a substantial amendment will be submitted to MREC and MHRA prior to implementation.

13.5 Planned Final Analyses

Final analysis of the trial is planned when all alive patients have been followed up for a minimum of 12 months after their last blinded treatment visit.

13.6 Bayesian Analyses

A Bayesian analysis will be conducted alongside the frequentist analysis of the TACE-2 trial data to provide additional information regarding the treatment effect both at interim and final analyses. The Bayesian analysis will be purely exploratory and complementary to the frequentist analysis and in no way will influence the decision-making process of the TACE-2 trial.

Bayesian analysis has been recommended for use in clinical trials (Parmar et al, Lancet 2001; Berry, Nature Reviews 2006) and provides a probability distribution for the true treatment effect (known as the posterior distribution) by combining current trial data with prior information. The treatment effect is usually expressed in the form of a hazard ratio

(HR) and in this study a HR<0.72 has been deemed to be clinically relevant. The prior information takes the form of a probability distribution for the true treatment effect prior to the trial results being generated and this can be based on clinical opinion (elicited or represented by 'off-the-shelf' distributions) or can be evidence-based. Alternatively, the analysis can use a non-informative prior in which case the trial data would dominate the analysis. A Bayesian approach can enable the following research questions to be answered: i) "what is the probability that there is a true treatment effect (i.e. HR<1) and that it is clinically relevant (i.e. HR≤0.72)?", ii) "what is the predicted result for the trial based on current evidence?" and iii) "what are the chances of getting a statistically significant result if we continue?". The aim in this study is to run a Bayesian analysis alongside the frequentist analysis of the TACE-2 trial data to provide complementary additional information regarding the treatment effect both at interim and final analyses.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Case Report Form

The Investigator or designee, will record data as accurately and completely as possible on each patient, as soon as the requested information is available. The Investigator will be responsible for the timing, completeness and accuracy of the patient's Case Report Form (CRF). The Investigator will supply the TACE-2 Trials Office with any required background data from such records.

The Table below gives the CRF reporting timelines to the Trial office:

Case Report Form:	**Time point**	**Timelines for completion & return to Trial office**
Randomisation Form	Randomisation	Within 1 month of randomisation
Eligibility Checklist	Randomisation	Within 1 month of randomisation
On study form	Randomisation	2-5 weeks post randomisation
Pre-TACE Form	Up to 72h pre-TACE	Within 2 weeks after TACE
Embolisation Form	At embolisation	Within 2 weeks after TACE
1 Week Post-TACE Form	1 week post TACE	Within 3 weeks after TACE
Follow-up Form	Week 10 post rand and 6 weekly thereafter	Within 1 month of scheduled visit
Progression Notification Form	When applicable	ASAP but within 7 days of becoming aware of progression

Disease Assessment Form	Week 10 post rand and 12 weekly thereafter	Within 1 month of scheduled visit
End of Study Treatment Form	End of study treatment	Within 2 weeks of event
Post Progression Follow-up Form	Routine follow-up visits post progression	Within 1 month of visit
Serious Adverse Event Form	When applicable	Within 24 hours of becoming aware of the event
Study Deviation form	When applicable	Within 2 weeks of event
Withdrawal Form	When applicable	Within 2 weeks of event
Death form	When applicable	Within 2 weeks of event

The database for the TACE-2 trial is a web based system that will allow electronic data entry at site via the website: https://www.cancertrials.bham.ac.uk/TACE2. Hospital staff involved in the trial will be provided with unique log in details to access the database and data validation will be provided through the database system. All data entered will be transcribed from the source data (see section 3.7).

The CRF may be amended during the course of the trial; this will not constitute a protocol amendment. Revised CRF will be circulated to participating sites with immediate effect; sites should ensure they are using the most recent version of the CRF.

Data reported on the CRF should be consistent with the source data (see section 3.8) or the discrepancies should be explained. If the information is not known, this must be clearly indicated e.g. by entering Not Known (NK) on the form.

The TACE-2 trial team at the University of Birmingham will be responsible for ensuring completeness of trial data. All missing or ambiguous data will be queried by email, telephone or writing to centres.

To maximise completeness of data, the site will be requested to call patients who have missed scheduled appointments for specific assessments and reschedule another appointment. For patients who have consented to take part in the quality of life study, the site will call patients who have not returned questionnaires to chase the questionnaire.

14.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc) at their site are

securely retained for at least 15 years after the end of the trial. Participating sites will be sent a letter specifying the permissible disposal date.

14.3 Centralised Computerised Records

Details of centres and participating staff will be recorded during the study onto a computer system at the Trials Office. Records of centres and participating staff will be modified to maintain accurate details of personnel and status held on the computer system. At the conclusion of the trial i.e. when all patient data has been collected and the analysis is complete, all the data stored on the computer system will be archived for 15 years after the completion of the trial. After trial conclusion, if any audit is required or new analysis to be performed, the data will be retrieved.

15 QUALITY MANAGEMENT

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU) according to the current guidelines for Good Clinical Practice (GCP). Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki.

15.1 Site Set Up

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition, all participating investigators will be asked to supply a current CV to the TACE-2 trials office. All members of the site research team will also be required to sign the Site Signature and Delegation log, which should be returned to the trials office. To participate in this study, the site's responsible investigator/radiologist must have performed ten or more TACE procedures according to local practice. Within the TACE-2 trial, TACE will be performed according to a standard protocol (see Appendix 7). Training in using DC Bead® will be given to the responsible investigator/radiologist and pharmacists at all centres if there is no previous experience in using this product before the site becomes activated.

Prior to commencing recruitment, all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File (ISF) and a Pharmacy File containing essential documentation, instructions and other documentation required for the conduct of the trial. The trials office must be informed immediately of any changes in the site research team.

15.2 Central Monitoring

Compliance with Protocol

The Trials Office will monitor participating centres electronic records for compliance with the protocol. The TACE-2 Trial Coordinator will be in regular contact with centre personnel (by phone/fax/email/letter) to check on progress and deal with any queries that may arise.

Verification of data

Data will be checked for missing or unusual values (range checks), timing and consistency over time. If any such problems are identified during in-house monitoring, a Data Clarification Form (DCF) specifying the problematic form within CRF will be returned to the local site. The correct data should be written on the DCF and signed by responsible person at the site (as assigned on the responsibilities form). The completed DCF should be returned to the Trials Office and the site should retain a copy of the DCF with the relevant correction.

15.3 On-Site Monitoring

Direct Access to Source Data/documents

Participating Investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data/documents as required.

Quality Assurance and Quality Control of Data

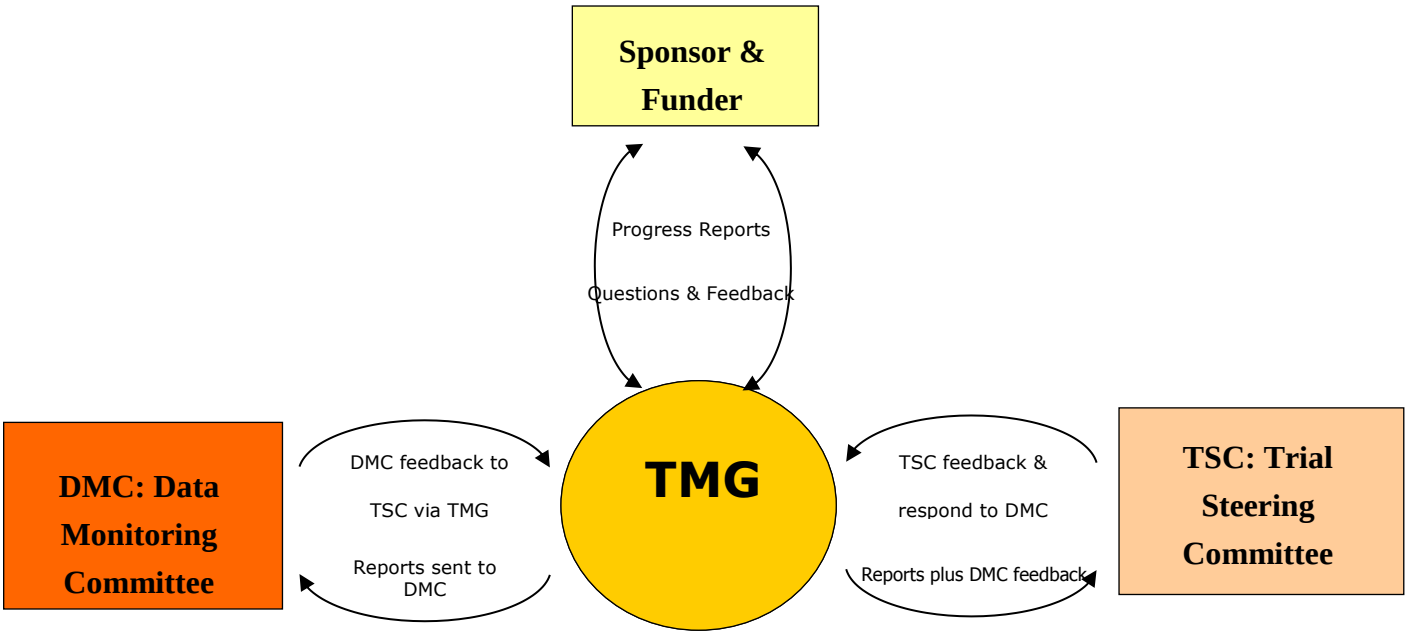
This study is being conducted according to the current guidelines for Good Clinical Practice. A sample of patients will be selected for source data verification throughout the trial. This may include random sampling, but may also include patients who might exhibit a reason for the data to be checked. Centres may be suspended from further recruitment in the event of serious and persistent non-compliance and/or very poor recruitment. Monitoring will be carried out according to the TACE-2 Quality Management Plan agreed by the sponsor. On-site monitoring will be carried out as required following a risk assessment and as documented in the TACE-2 Quality Management Plan. If a monitoring visit is required, the site will be contacted to arrange a suitable date.

16 END OF TRIAL DEFINITION

For regulatory and ethical purposes, the trial will be closed to recruitment when 206 patients have been recruited to each treatment arm. However, the study may close to recruitment prior to this milestone based on the planned formal interim analysis. The study will continue for one year after the last patient has been recruited.

17 STUDY ORGANISATIONAL STRUCTURE

17.1 Relationship Between Committees and the Sponsor



17.2 Trial Management Group

The Trial Management Group (TMG) is comprised of the Chief Investigator and other collaborators as detailed on page 3. The TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in person as required.

17.3 Trial Steering Committee

A Trial Steering Committee (TSC) will provide overall supervision for the trial and provide advice through its independent chair. Membership includes an independent oncologist, hepatologist and statistician plus the Chief Investigator or deputy. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet at least once a year or more often if required.

17.4 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been established for this study. Membership includes an independent oncologist, surgeon and statistician. The main objective of the DMC will be to advise the TSC whether there is any evidence to advise that the study should be amended or terminated, based on the current data. Only the trial

statistician and DMC members will see the confidential unblinded analyses of outcome by treatment group. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

18 ETHICS AND GOOD CLINICAL PRACTICE

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments. Copies of the declaration may be obtained from WMA website: http://www.wma.net/e/policy/b3.htm. The trial will be conducted in accordance with the principles of Good Clinical Practice according to the EU directive 2005/28/EC (GCP Directive) and The Medicines for Human Use (Clinical Trials) Regulations Statutory Instruments 2004/1031 and 2006/1938 in the UK.

The sponsor will ensure appropriate regulatory and ethical approval will be gained for the study in each Member State concerned prior to patient recruitment in that Member State. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval in the Member State concerned prior to circulation to sites.

The Sponsor, or delegated representative, will ensure an annual trial update report and the annual safety report is sent to the relevant Ethics Committee/s in Member States concerned. SUSARs and SARs will be reported in accordance with EU Directive 2001/20/EC (see Section 10).

18.1 Site Specific Assessment and Trust approval

For UK centres, before enrolling patients into the study, the Principal Investigator or designee must apply for Site Specific Assessment from Trust Research & Development (R&D) and be granted NHS approval. Sites will not be permitted to enrol patients until written confirmation of Trust R&D approval is received by the TACE-2 Trials Office. It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

For centres outside the UK, before enrolling patients into the study and subsequent amendments, the Principal Investigator or designee must apply for favourable opinion within their IRB/IEC requirements.

18.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from each patient prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the trial. For details of informed consent procedure see section 5.

18.3 Patient's Right to Withdraw

A patient has the right to withdraw from the trial without giving reasons and without prejudicing his/her further treatment. See Section 4 for more details regarding withdrawal.

19 CONFIDENTIALITY AND DATA PROTECTION

The personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Directive 95/46/EC and the Data Protection Act 1998 for UK sites (www.opsi.gov.uk/acts/acts1998/19980029.htm)

To preserve the patient's anonymity, the unique trial number, their initials, date of birth, and hospital name and/or number will be recorded on the case report forms. The Principal Investigator must ensure the patient's anonymity is maintained. The Principal Investigator must maintain documents not for submission to the TACE-2 Trials Office in strict confidence.

The Trials Office will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified.

Patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

20 FINANCE, INSURANCE AND INDEMNITY

20.1 Finance

This study is a clinician-initiated and clinician-led study supported by the NIHR and funded by educational grants from Bayer and Biocompatibles UK. Sorafenib and matching placebo will be supplied at no cost by Bayer and free DC Bead® will be supplied by Biocompatibles UK.

20.2 Indemnity & Insurance

This study is a clinician-initiated and clinician-led study sponsored by the University College London.

The University College London (UCL), holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent.

However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or liability for any negligence on the part of the employees of hospitals. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

21 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University College London, University of Birmingham, Bayer and Biocompatibles UK. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1: Diagnosis of HCC: AASLD CRITERIA

Diagnosis of suspected HCC may be confirmed by biopsy or by application of the following non-invasive diagnostic criteria that have been proposed by the AASLD. Reference: Bruix, J and Sherman, M. Management of Hepatocellular carcinoma. *Hepatology* (2005). 42(5):1208-36.

1. Nodules between 1-2 cm found on ultrasound screening of a cirrhotic liver should be investigated further with two dynamic studies, either CT scan, contrast ultrasound or MRI with contrast. If the appearances are typical of HCC (i.e. hypervascular with washout in the portal/venous phase) in two techniques the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not coincidental among techniques the lesion should be biopsied.

2. If the nodule is larger than 2 cm at initial diagnosis and has the typical features of HCC on a dynamic imaging technique, biopsy is not necessary for the diagnosis of HCC. Alternatively, if the AFP is >200 ng/mL biopsy is also not required. However, if the vascular profile on imaging is not characteristic or if the nodule is detected in a non-cirrhotic liver, biopsy should be performed.

APPENDIX 2: RECIST CRITERIA

The following contains excerpts from the RECIST criteria plus trial specific instructions.

For more information regarding RECIST and a full copy of criteria, go to http://www.eortc.be

Ref. E.A. Eisenhauera, P. Therasseb, J. Bogaertsc *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). 45, 228-247 (2009).

NOTE All imaging will be independently reviewed by IXICO to confirm response or progression

1. Measurability of Tumour Lesions at Baseline

1.1 Definitions

Only patients with measurable disease at baseline should be included. At baseline, tumour lesions will be categorised as follows:

Measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] with a minimum size of 10mm by CT scan (CT scan slice thickness no greater than 5mm), 10mm caliper measurement by clinical exam and 20 mm by chest X-ray. For malignant lymph nodes to be considered pathologically enlarged and measureable, a lymph node must be ≥15 mm in short axis when assessed by a CT scan (at baseline and in follow-up, only the short axis will be measured and followed).

Nonmeasurable (all other lesions, including small lesions [longest diameter <10 mm or pathological lymph nodes with ≥10 to >15mm short axis] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease,

lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumour lesions that are situated in a previously irradiated area are not be considered measurable

1.2 Specifications by methods of measurements

The same method of assessment and the same technique should be used to characterise each identified and reported lesions at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti tumour effect of a treatment. The following examinations are allowed in the TACE-2 study for determining response and progression free survival:

CT and MRI: Dynamic phase contrast enhanced CT or MRI should be used so that arterial enhancement and venous phase washout can be demonstrated. CT and MRI are the best currently available and reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm; this specification applies to tumours of the chest, abdomen and pelvis, while head and neck tumours and those of extremities usually require specific protocols. More details concerning the use of this method of assessment can be found in Appendix II of RECIST criteria.

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. More details concerning the use of this method of assessment can be found in Appendix II of RECIST criteria.

2 Tumour Response Evaluation

2.1 Baseline evaluation

2.1.1 Baseline documentation of "target" and "nontarget" lesions

All measurable lesions up to, a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as “target” lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as "nontarget" lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

2.2 Response criteria

A Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to this, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more lesion is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

B Evaluation of nontarget lesions

Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [1]

[1]To achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increase sufficiently to merit discontinuation of therapy (examples can be found in Appendix II of RECIST criteria).

C Evaluation of best overall response

The best overall **response** is the best **response** recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best **response** assignment will depend on the achievement of both measurement and confirmation **criteria.**

Table 1: Overall responses for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

2.2.1 Frequency of tumour re-evaluations

For the TACE-2 trial, Progression Free Survival (PFS) and disease control (CR+PR+SD) will be evaluated clinically and radiologically by a CT scan of the abdomen and chest at baseline, week 10, week 22 and then at 3 monthly intervals until progression or end of study or death.

3 Reporting Of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response**,** 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database)

All of the patients who met the eligibility **criteria** should be included in the main analysis of the **response** rate. Patients in **response** categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the **response** rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g. early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

APPENDIX 3: ECOG PERFORMANCE STATUS SCALE

ECOG Status	Description
0	Asymptomatic, fully active and able to carry on all predisease performance without restrictions
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, e.g., light housework, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours but not bedridden.
4	Completely disabled. Cannot carry on any self-care. Totally bedridden.
5	Dead

References:

Karnovsky DA. Meaningful clinical classification of therapeutic responses to anti-cancer drugs: Editorial. Clinical Pharmacology and Therapeutics 1961; 2: 709-712

Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. JNCI 1980; 65: 25-32.

APPENDIX 4: Child-Pugh Score

Child-Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

Parameters	Points assigned to laboratory values and signs		
	1	2	3
Laboratory value			
Total serum bilirubin level	<2 mg per dL (<34 µmol per L)	2 to 3 mg per dL (34 to 50 µmol per L)	>3 mg per dL (>50 µmol per L)
Serum albumin level	>3.5 g per dL (>35 g per L)	2.8 to 3.5 g per dL (28 to 35 g per L)	<2.8 g per dL (<28 g per L)
International Normalized Ratio	<1.70	1.71 to 2.20	>2.20
Signs			
Ascites	None	Suppressed with medication	Refractory
Encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Based on total points, a patient with cirrhosis is assigned to one of three classes:

Child class A = 5 to 6 points;

Child class B = 7 to 9 points;

Child class C = 10 to 15 points

APPENDIX 5: NCI Common Terminology Criteria for Adverse Events

Adverse Events will be recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE (v4))

The full NCI CTCAE (v4) document is supplied in the Investigator Site Folder and can also be requested form the TACE-2 Trials Office.

It is also available on the National Cancer Institute (NCI) website, at the following address:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX 6: STAGING: NEW YORK HEART ASSOCIATION (NYHA)

Class 1: Subjects with no limitation of activities; they suffer no symptoms from ordinary activities

Class 2: Subjects with slight, mild limitation of activity; they are comfortable with rest or mild exertion

Class 3: Subjects with marked limitation of activity; they are comfortable only at rest

Class 4: Subjects who should be at complete rest, confined to a bed or chair; any physical activity brings on discomfort and symptoms occur at rest

APPENDIX 7: SUPPLEMENTARY LOADING INSTRUCTIONS

The instructions are for a maximum dose of **150mg** to be delivered in 2 vials of DC Bead® (100-300 and 300-500µ**m** vials depending on lesion size(s) and degree of vascularity). 500-700µ**m** vials may be used in a minority of cases in large hypervascular tumours or in the presence of arterio-portal or arterio-venous shunts. Each vial will contain 75mg doxorubicin at a dose of 37.5**mg** per ml of DC Bead®. Doxorubicin powder for reconstitution is available as 50mg vials, and it is these vials that are recommended for use. DC Beads® are suitable for loading doxorubicin-HCl ONLY. Liposomal formulations of doxorubicin are not suitable for loading into DC Beads®. The instructions are to load **150mg** doxorubicin into two vials of DC Bead®:

- **DOXORUBICIN LOADING SOLUTION**

Loading and preparation of DC Bead® must be carried out using strict aseptic technique under controlled conditions. Reconstitute **3** x 50mg vials of doxorubicin by adding **2ml** of sterile water for injection to each vial. Mix well to obtain a clear solution this usually takes 2-3 minutes. The doxorubicin concentration in each reconstituted vial is 25.0mg/ml.

- **PREPARATION OF DC BEAD®**

(a) Remove as much saline as possible from each vial of DC Bead® using a syringe with a small gauge needle. This usually takes 5-10 minutes depending on experience.

- **LOADING OF DC BEAD®**

(b) Using a syringe and needle add a total of **3.0ml** of reconstituted doxorubicin solution directly into each vial (100-300µ**m,** 300-500 µ**m** or 500-700 µ**m**) of DC Bead®.

(c) Agitate the DC Bead®/doxorubicin solution gently to encourage mixing then allow to stand until DC Bead® are red and the solution is almost colourless. For this static loading the following times should be used to give at least 98% loading of the dose into DC Bead®:

Product Cap Colour	Nominal Size Range (µm)	Time to give >98% Loading
	100-300	45 mins
	300-500	90 mins
	500-700	90 mins

(d) DC Bead® may be loaded with doxorubicin overnight in a fridge at 2-8˚C, and kept up to 14 days in the fridge. Microbiological stability is the responsibility of the user.

PREPARATION FOR USE

(a) Prior to use, aspirate the free fluid and add 10-20mls of non-ionic contrast media to each vial and transfer each of the two vials of DC Bead® loaded with doxorubicin to a separate syringe. This will take 2-15 minutes again depending on experience. Invert the syringe gently to obtain an even suspension of DC Bead®.

(b) The suspension of loaded DC Bead® is physically and chemically stable for 14 days or 7 days once mixed with contrast. The suspension must be kept in sterile conditions to ensure microbial stability.

(c) A pink coloration will be present in the suspension as approximately 0.3% (0.1mg) of the loaded drug elutes into the contrast media suspension.

ADDITIONAL INFORMATION

- DC Bead® should be loaded with doxorubicin prior to use. Loading of DC Bead® can take 1-2 hours depending on Bead size, but can be loaded and kept up to 14 days in the fridge. However once non ionic contrast media is added to the doxorubicin loaded DC Bead®, the mixture should be used within 7 days.
- Non-ionic contrast media recommended by Biocompatibles is Omnipaque, however any non-ionic contrast media can be used, with the exception of lipiodol. Lipiodol is NOT to be used with DC Bead®
- Once loaded, each syringe will contain the loaded bead mixed with 10-20mls of non-ionic contrast.

Transarterial Chemoembolisation using DC Bead®

It is recommended that TACE using DC Bead® is performed according to instructions below:-

- A maximum 150mg flat doxorubicin dose to be used. The actual volume of DC Bead® delivered is at the discretion of the radiologist
- When injecting into a particular area of liver, the smaller 100-300μm DC Bead® should be injected first, followed by larger 300-500μm DC Bead®
- Delivery of DC Bead® should be performed slowly in small aliquots (e.g. 1ml/min) to avoid reflux
- The DC Bead® should be divided between the lesions (where there is more than one). The volume of DC Bead® injected to each lesion will be at the discretion of the radiologist but should reflect the size of the individual lesion with respect to the total tumour bulk

- In the case of extensive bilobar disease in which a single session treatment could lead to liver decompensation, treat only one lobe. The second lobe should be treated ideally within 2-3 weeks
- For embolisation, we recommend the use of a superselective technique and aim for sluggish flow in the main feeding vessels with statis in the intra and peri lesional branches. If the embolisational endpoint is not reached after the first vial is delivered, pull the catheter back a few millimetres, then inject the second vial. The use of bland embolic is not advised
- ®In some cases (e.g. smaller or hypervascular tumours) it may not be possible to deliver the full 2 vials of DC Bead®. DO NOT OVEREMBOLISE. Injection should be stopped when the embolisation endpoint has been achieved even if the full 4ml of DC Bead® is not delivered
- If the tumour is large and hypervascular or these is arterio-portal or arterio-venous shunting larger 500-700μm beads can be used
- Antibiotic cover should be provided according to local practice
- Meticulous attention to vascular anatomy is important. Avoid non target embolisation. Identify cystic, gastric, duodenal and pancreatic branches and avoid reflux into or embolisation of these branches
- As selective embolisation is often required, many cases will necessitate the use of microcatheters. However, in some cases with large feeding vessels, the procedure may be able to be performed with 4Fr conventional catheters

APPENDIX 8: QUALITY OF LIFE: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_| |_|_| |_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_| |_|_| |_|_|_|_|

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

During the past week:

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

Please go on to the next page

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

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 9: QUALITY OF LIFE: EORTC QLQ-HCC18

EORTC QLQ-HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced the following symptoms or problems during the past week. Please answer by circling the number that best applies to you.

Please fill in your initials: _____

Your birth date: _____

Today's date: _____

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
1. Did you feel thirsty?	1	2	3	4
2. Have you had problems with your sense of taste?	1	2	3	4
3. Have you lost muscle from your arms or legs?	1	2	3	4
4. Have you had abdominal swelling?	1	2	3	4
5. Have you been bothered by the appearance of your abdomen?	1	2	3	4
6. Have you been bothered by your skin or eyes being yellow (jaundiced)?	1	2	3	4
7. Have you had itching?	1	2	3	4
8. Have you had pain in your shoulder?	1	2	3	4
9. Have you had abdominal pain?	1	2	3	4
10. Have you had fevers?	1	2	3	4
11. Have you had chills?	1	2	3	4
12. Have you worried about getting enough nourishment?	1	2	3	4
13. Have you felt full up too quickly after beginning to eat?	1	2	3	4
14. Have you worried about your weight being too low?	1	2	3	4
15. Have you been less active than you would like to be?	1	2	3	4
16. Have you found it difficult to keep going or to finish things you started?	1	2	3	4
17. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
18. Have you been bothered by the effect of the disease or treatment on your sex life?	1	2	3	4

APPENDIX 10: EUROQOL EQ-5D HEALTH QUESTIONNAIRE

By placing a tick in one box in each group below, please indicate which statements best describe your health state today

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

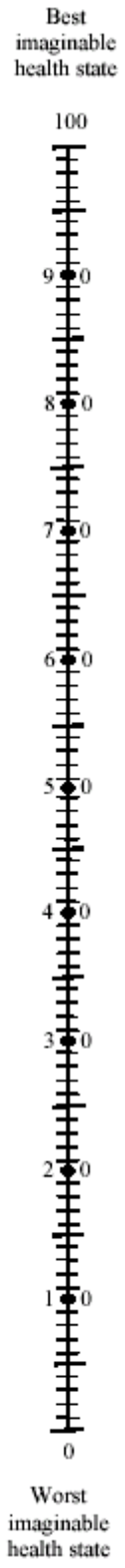
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health is today.

Your own heatlh state today



APPENDIX 11: EXPECTED ADVERSE EVENTS

Very Common or Common Events		TACE using DC Bead® loaded with Doxorubicin	Sorafenib
Haematological	Lymphopenia		√
	Leucopenia	√	√
	Neutropenia	√	√
	Thrombocytopenia	√	√
	Anaemia	√	√
Gastrointestinal	Anorexia	√	√
	Weight decreased		√
	Increased amylase		√
	Increased lipase		√
	Dyspepsia		√
	Dysphagia		√
	Gastroesophageal reflux disease		√
	Diarrhoea	√	√
	Nausea	√	√
	Vomiting	√	√
	Constipation		√
	Stomach aches	√	
	Perforation		√
	Stomatitis	√	√
Renal	Nephrotoxicity	√	
	Renal Failure		√
	Proteinuria		√
Respiratory	Rhinorrhoea		√
	Dysphonia		√
Hepatic	Liver dysfunction/failure	√	
	Abnormal liver transaminases	√	
	Transient increase in transaminases		√
Infection	Liver abscess	√	
	Infections		√
	Folliculitis		√
Endocrine	Hypothyroidism		√
Neurotoxicity	Peripheral neuropathy	√	√
	Dysguesia		√
Ear disorders	Tinnitus		√

	Ocular toxicity	√	
Cardiac Disorders	Congestive heart failure		√
	Myocardial ischaemia and infarction		√
	Cardiotoxicity	√	
Skin disorders	Dry skin		√
	Rash	√	√
	Alopecia	√	√
	Hand foot skin reaction		√
	Erythema		√
	Pruritus		√
	Keratocanthoma/squamous cell skin cancer		√
	Dermatatis exfoliative		√
	Acne		√
	Skin desquamation		√
	Hyperkeratosis		√
Musculoskeletal	Myalgia		√
	Muscle spasms		√
	Arthralgia		√
Other	Raised temperature	√	√
	Haemorrhage	√	√
	Pain	√	√
	Hypertension		√
	Hypophosphataemia		√
	Hypocacalcaemia		√
	Hypokalaemia		√
	Hyponatraemia		√
	Depression		
	Fatigue		√
	Flushing		√
	Erectile dysfunction		√
	Asthenia		√
	Influenza-like illness		√

Uncommon/Rare Events	TACE using DC Bead® loaded with Doxorubicin	Sorafenib
Hypersensitivity reactions/anaphylaxis		√
Angioedema		√
Hyperthyroidism		√
Dehydration		√
Reversible posterior leukoencephalopathy		√
QT prolongation		√
Hypertensive crisis		√
Interstitial lung disease events		√
Pancreatitis		√
Gastritis		√
Gastrointestinal perforations		√
Increase in bilirubin and jaundice		√
Drug induced hepatitis		√
Cholecystitis/cholangitis		√
Eczema		√
Erythema multiforme		√
Radiation recall dermatitis		√
Stevens-Johnson syndrome		√
Toxic epidermal necrolysis		√
Leucocytoclastic vasculitis		√
Rhabdomyolysis		√
Nephrotic syndrome		√
Gynaecomastia		√
Transient increase in blood alkaline phosphatase		√
Abnormal INR/prothrombin level		√

Unknown Frequency		
Encephalopathy		√

APPENDIX 12: FLOWCHART OF ASSESSMENTS

	Screening (within 28 days prior to rand.)	**Day 1** (day of randomisation)	Up to 72 hours Pre-TACE	TACE Day 0	TACE Day +1	TACE Day+7	**Week 10** (post randomisation)	**Week 16** (post randomisation)	**Week 22** (post randomisation)	**Every 6 WEEKS thereafter** (until week 22 then as per standard of care thereafter)
Informed consent	x									
Confirmation of diagnosis of HCC according to AASLD guidelines or histology	x									
Medical history includes prior surgery, prior chemo/radiation, allergy, cardiac history	x									
Toxicity assessment			x			x	x	x	x	x
Physical examination including vital signs, height, weight and physical exam of organ systems	x	x	x				x	x	x	x
Blood pressure	x	x	x			x	x	x	x	x
ECOG performance status	x	x	x			x	x	x	x	x
Concomitant drug history	x	x	x				x	x	x	x
Full blood count and clotting (PT, INR) and Serum biochemistry[1]	x	x	x			x	x	x	x	x
Alpha fetoprotein	x	x	x				x	x	x	x
Hepatitis B and C antigen and antibody	x									
Amylase	x									
ECG	x		x			x	x	x	x	x
LVEF determined by either MUGA scan or echocardiogram	x									
Chest CT and dual phase CT or contrast enhanced MRI scan of abdomen[2]	x						x		x	
Documentation of Child-Pugh score	x	x	x			x	x	x	x	x
QoL assessment		x[3]	x				x	x	x	x
Pregnancy test in women of child bearing potential	x									
Collection of Biomarker blood	x	x	x		x		x		x	
Arrangements for TACE to be performed within 2-5 weeks from randomisation		x								
Commence study drug - sorafenib or placebo		x								
TACE				x						

1 Biochemistry to include Urea, Cr, Na, K, Ca, Alb, Bili, Aphos, ALT (or AST), GGT

2 CT scans to be performed at every 12 weeks (coincides with visits at weeks 10, 22, etc) until week 22 and as per local standard of care thereafter. To ensure comparability, the baseline X-rays/CT scans and subsequent X-rays/CT scans must be performed using identical tech scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Each lesion must be followed with the same method throughout the study (from baseline until progression).

3 QoL questionnaire should be administered before randomisation or at randomisation, before the patient is informed of the treatment to which he is assigned.

APPENDIX 13: PATIENT DIARY

Patient Diary

To be completed by Research Nurse:

PATIENT DETAILS:

Trial No: ☐☐☐ Patient Initials: ☐☐ Date of Birth: ☐☐ / ☐☐☐ / ☐☐☐☐

(dd/mmm/yyyy)

Randomising Hospital: ……...

Treatment Hospital:……

DETAILS OF TREATMENT CYCLE:

Start Date: *(dd/mmm/yyyy)* ☐☐ / ☐☐☐ / ☐☐☐☐

Starting Dose of Trial Treatment *(mg per administration)* ☐☐☐ mg

NOTE: before issuing the patient diary sheet at each visit, please complete the relevant information on the following pages, including the numbers of each tablet to take (at the top of the sheet) and the date of each dose due (in the table).

Dear Patient,

Please use this sheet to keep a record of your tablets as you take them. You will be taking trial treatment tablets _______ a day.

Each dose of ____ **mg** is made up from: _____ **x 200 mg tablet(s)**

Swallow the tablets with water at least 1 hour before or 2 hours after eating. Please record the time that you take each dose. If you miss a dose, record this by writing "missed" on the sheet. If you miss a dose of trial treatment, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once.

Date: (nurse to complete)	**Morning Dose:** please record time taken	**Evening Dose:** please record time taken	**Additional Notes:** (e.g. please note any side effects or any reasons for missing a dose)
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	

Date: (nurse to complete)	**Morning Dose:** please record time taken	**Evening Dose:** please record time taken	**Additional Notes:** (e.g. please note any side effects or any reasons for missing a dose)
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
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___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	

Date: (nurse to complete)	**Morning Dose:** please record time taken	**Evening Dose:** please record time taken	**Additional Notes:** (e.g. please note any side effects or any reasons for missing a dose)
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
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___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	
___/___ /__	____ : ___ am	___ : ___ pm	

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS DIARY.

Please give the completed diary to the nurse at your next hospital visit.