ABC-07

Addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced biliary tract cancers

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Please note: This trial protocol must not be applied to patients treated outside the ABC-07 trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

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1. PROTOCOL SUMMARY

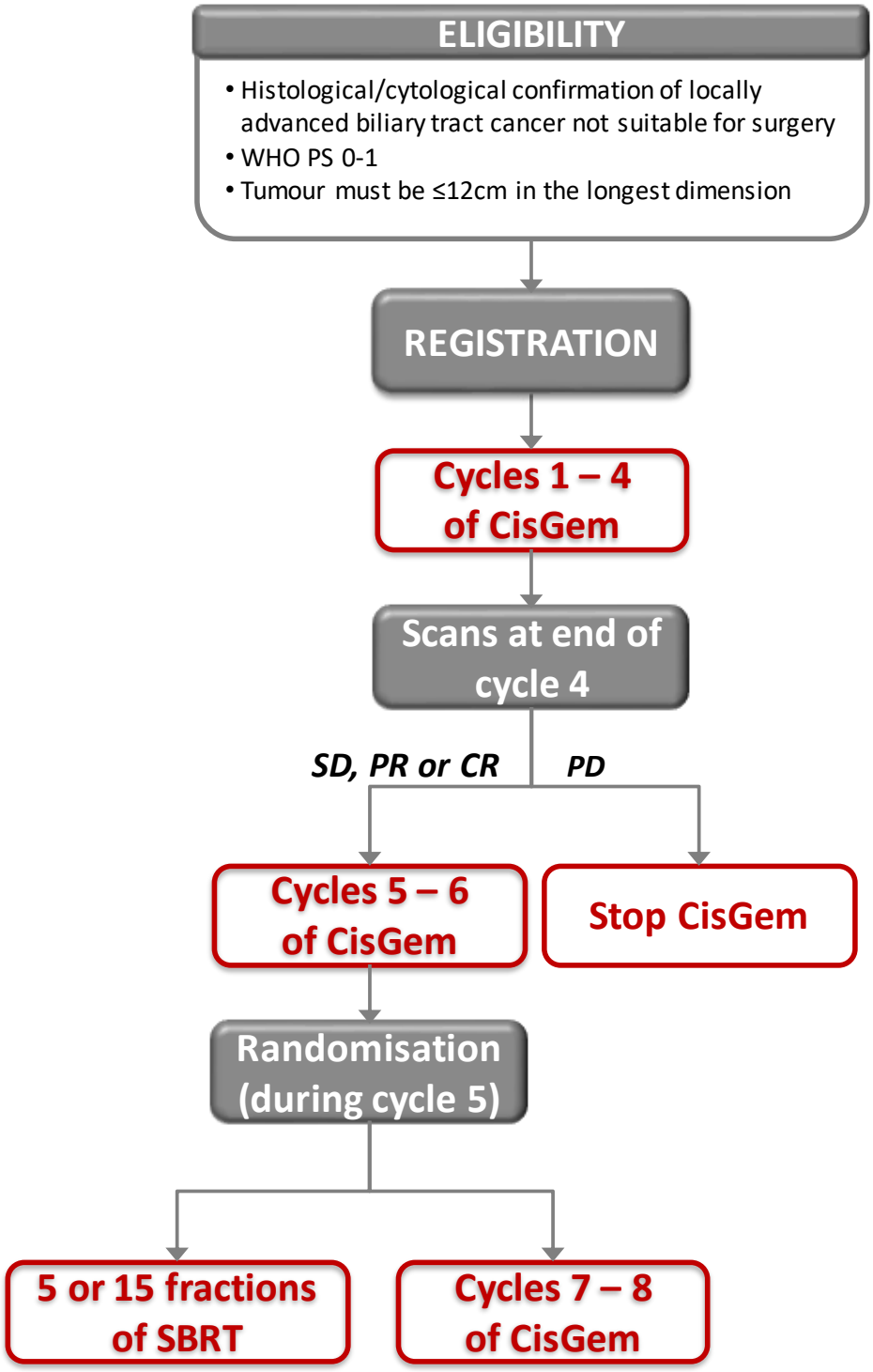
1.1. Summary of Trial Design

Title	Addition of stereotactic body radiotherapy (SBRT) to systemic chemotherapy in locally advanced biliary tract cancers
Short Title/acronym	ABC-07
EUDRACT Ref	2014-003656-31
Sponsor name & Reference	University College London; UCL 14/0174
Funder name & Reference	Cancer Research UK; A18752
Design	Multicentre phase II study (with a feasibility stage) with 2:1 randomisation between cisplatin and gemcitabine (CisGem) chemotherapy + SBRT and CisGem chemotherapy alone, respectively
Overall aim	**Feasibility:** The overall aim of the feasibility component of the trial is to determine if it is feasible to deliver SBRT in a multicentre trial setting in a rare disease. In particular, will clinicians recruit to the trial and will sufficient patients accept randomisation. If the feasibility component proves successful, the trial would continue into the full phase II trial. **Phase II:** The overall aim of the phase II trial is to evaluate the efficacy of 6 cycles of CisGem chemotherapy followed by SBRT compared to 8 cycles of CisGem.
Target accrual	**Feasibility:** Approximately 18 patients with locally advanced inoperable cholangiocarcinoma. **Phase II:** 81 patients with locally advanced inoperable cholangiocarcinoma, which will include the patients recruited in the feasibility stage.
Primary endpoint	**Feasibility:** An average recruitment rate of at least 1 patient per month once 6 sites have been activated. **Phase II:** To evaluate the relative merits of adding SBRT to CisGem chemotherapy in terms of progression free survival.
Secondary endpoints	**Feasibility & Phase II:** • Progression free survival at 9 months after randomisation • Worst grade of AE (CTCAE v4.03) • Best overall response rate (according to RECIST v1.1 criteria) • Progression free survival • Duration of response • Overall survival • Patterns of treatment failure • Time to treatment failure • Achieving downstaging facilitating surgery • Quality of Life (EQ 5D and EORTC QLQ- BIL21)

Exploratory Biological Studies	The following types of samples will be collected and stored for future research: • Archival paraffin-embedded tissue • Whole blood for ctDNA • Whole blood for germline DNASerum samples (optional for trial sites)
Inclusion & Exclusion Criteria *(Refer to 6.2* Patient Eligibility - REGISTRATION *for the full list of eligibility criteria)*	The main inclusion criteria are: • A histopathological/cytological diagnosis of locally advanced, non-resectable biliary tract carcinoma (intra- or extra-hepatic), (excluding cancer of the gall bladder and ampullary carcinoma) • Not suitable for radical surgery, or medically unfit for surgery as decided by a hepatobiliary MDT • Measurable disease (according to RECIST criteria v1.1). (If disease is not measurable using RECISTv1.1, tumour must be visible for targeting with radiation). • Tumour (and nodes if involved) visible on cross-sectional imaging ≤12 cm in the longest dimension. For patients with non-measurable disease, sites should use the CT reconstructions (coronal or sagittal views) to measure tumour size. • Adequate biliary drainage • WHO PS 0 or 1 • Adequate bone marrow, renal & liver function • Life expectancy >12 weeks • 16 years or over • Patient consent The main exclusion criteria are: • Metastatic disease • Direct tumour extension in the duodenum, stomach, small bowel or large bowel • Previous abdominal radiotherapy or previous selective internal radiotherapy such as hepatic arterial Yttrium therapy • Previous hypersensitivity to platinum salts • Uncontrolled systemic disease (diabetes with established sensory peripheral neuropathy) • Other/prior malignancy or intercurrent disease precluding trial entry • Other concomitant anti-cancer therapy (except steroids) • Pregnancy/breast-feeding
Number of sites	Approximately 18 sites (to include SBRT sites and recruiting sites) within the UK
Treatment summary	All patients will be **registered** to receive 6 cycles of chemotherapy consisting of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-day cycle. Patients will then be **randomised** to receive either: **Investigational arm:** 5 or 15 fractions of SBRT given over 5-21 days (number of fractions and duration of therapy depends on the size of the tumour as measured on the end of cycle 4 imaging scan). SBRT should start not

	more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy. Or **Standard arm:** 2 further cycles of CisGem (8 cycles in total)
Anticipated duration of recruitment	**Feasibility:** 18 months **Phase II:** Up to 6 years (including feasibility)
Duration of patient follow up	Patients will be followed up 3-monthly until disease progression or for up to two years after registration. Following progression patients will be followed up as per standard practice and survival data will be collected.
Definition of end of trial	For regulatory purposes the end of the trial will be two years after enrolment of the final patient or once all patients have died, whichever happens first.
Radiotherapy Quality Assurance	Quality Assurance will be conducted by the National RTTQA group. Pre-trial QA will involve a radiotherapy specific protocol and a pre-trial test case will be delineated by all participating investigators and planned by the corresponding RT department – feedback will be provided on the delineated volumes and plan prior to patients being entered into the trial. In addition, this study requires a rapid review of segmented GTV and normal tissue and radiotherapy plans prior to delivery of radiation treatment for at least the first 3 patients to be treated in each SBRT site, including at least one patient with a tumour ≤6cm and at least one patient with a tumour >6cm.
Central imaging Quality Assurance	Central review of CT images (and additional imaging if required) will be performed for 100% of patients from each centre, to exclude patients who have not been randomised. Images from registration up until 6 month follow up would be reviewed. The following sets of scan images (CT, and MRI if available) should be pseudonymised and sent for central assessment to confirm disease status: baseline (pre-registration), end of cycle 4, completion of treatment, 3 and 6 month follow-up and confirmation of disease progression scan (if applicable).

1.2. Trial Schema



CisGem: *Cisplatin 25 mg/m² plus gemcitabine 1000 mg/m² on days 1 and 8 of a 21-day cycle*
SBRT:
Tumours ≤6cm: 50Gy, 45Gy or 40Gy of stereotactic body radiotherapy (SBRT) delivered in 5 fractions over 5 -15 days. The time between fractions should be 24 to 72 hours (preferred interval of 48 hours).
Tumours >6cm and ≤12cm: 45Gy, 58.1Gy or 67.5Gy of SBRT delivered in 15 consecutive daily fractions, delivered on weekdays over 19-21 days

2. INTRODUCTION

2.1. Background

Biliary tract cancers (BTC) are uncommon cancers comprising of cholangiocarcinoma (intrahepatic, hilar and extrahepatic), gallbladder and ampullary cancers. They account for 3% of all gastro-intestinal cancers globally.

There has been an increase in the incidence of cholangiocarcinoma since the early 1970s, increasing 16-fold between 1971-1973 and 1999-2001 in England & Wales (cancer stats UK web accessed 5 March 2014 http://www.cancerresearchuk.org/). A review of English [1] patients diagnosed between 1998 and 2007 (extracted from the National Cancer Data Repository) showed that there were 12,638 patients diagnosed with biliary cancer; 21.4% [20.6-22.2%] survived 1 year and only 3.8% [3.3–4.2%] survived 5 years after diagnosis.

Surgery is the only potentially curative modality for patients with BTC and survival is better in patients achieving clear resection margins with a 5-year survival rate of 19-47% (versus 0-12% in patients with histologically-involved margins) [2-4] and 3-year survival rate varying from 36%-53% [5-7].

2.2. Cisplatin and Gemcitabine in the Treatment of BTC

Between 2005 and 2009, the National Cancer Research Institute (NCRI) Upper Gastrointestinal Clinical Studies Group (CSG) conducted the ABC-02 trial, a randomised phase III design evaluating the benefit of gemcitabine with or without cisplatin in advanced or metastatic BTC. The ABC-02 data was combined with data from a previous randomised phase II study with an identical design (ABC-01 [8]). This pre-planned analysis of the combined data demonstrated an improvement in overall survival (OS; from 8.3 to 11.7 months hazard ratio 0.64 [95% CI 0.52 – 0.80, p<0.001]), progression-free survival (PFS; from 5.0 to 8.0 months, p<0.001) and tumour control rate (radiological stable disease, partial or complete response, 71.8% to 81.4%, p=0.049) [9]. This improvement was achieved with no significant increase in toxicity and improved quality of life. The ABC-02 study has established cisplatin and gemcitabine (CisGem) as the standard of care for advanced BTC as well as providing a backbone for subsequent studies. A meta-analysis has confirmed that CisGem combination is the 1st line standard of care in good performance status (PS) patients regardless of ethnicity, in both intra and extrahepatic tumour locations.

2.3. Loco-regional Treatments for BTC

Currently the standard of care for unresectable BTC is CisGem, however there is no current standard for local, liver directed therapy despite the observation that local (primary tumour) and regional recurrences are the most common patterns of relapse in BTC [10]. The optimal radiation dose in the definitive treatment of biliary malignancies is unknown, however higher dose radiotherapy (RT) approaches that use either a combination of transcatheter brachytherapy plus external beam radiation therapy (EBRT), three-dimensional conformal radiation therapy (3D-CRT), or intensity modulated radiation therapy (IMRT) with or without chemotherapy may be associated with better local control (LC) and possibly prolonged survival [7, 11]. Advances in imaging and radiation technology delivery such as image guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT) now permit tumoricidal doses of radiation to be delivered safely [12, 13].

2.4. Role of Radiotherapy in BTC Management

The evidence regarding the use of radiotherapy in cholangiocarcinoma is scarce. Aitken et al [14] have recently undertaken a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) systematic review of the role of radiotherapy in primary liver malignancies and conclude: “SBRT is a promising technique in the locally advanced setting, with the dual advantages of enabling dose escalation whilst minimizing time off systemic therapy and requires further investigation.”

Published reports describing radiotherapy response are generally of non-randomized, single institution experiences that are subject to selection bias. Patients with better performance status may receive higher radiation doses. Reports of patients receiving EBRT for bile duct carcinoma have suggested that doses of 40 to 45 Gy result in improved survival outcomes compared to lower doses. The largest single institution retrospective reviews are over several decades (Crane et al [15] and Farley et al [16]). Chen et al [17] reported on 84 patients with histologically-proven unresectable intrahepatic cholangiocarcinoma; 35 patients received RT and 49 did not. There were no differences in the 2 groups regarding age, gender, stage, tumour size and multifocality. Doses ≥50 Gy in 2Gy/fraction were delivered in 30/35 cases. At the first follow-up (~6weeks) disease control was achieved in 85.7% of the patients (3 patients had a CR, 10 PR, 17 SD). One- and two-year survivals for the radiation group and non-radiation groups were 38.5% vs 16.4% and 9.6% vs 4.9%, respectively. This study suggests that radiotherapy might have some benefit in intrahepatic cholangiocarcinoma, but conclusions are severely limited by the heterogeneous population, the lack of chemotherapy, the retrospective nature of the study, and non-standardisation of the radiotherapy dose. The poor survivals also reflect the lack of chemotherapy use.

Kim et al [11] reported on 92 patients with unresectable intrahepatic cholangiocarcinoma between 2001-2012; 25 (27.1%) received capecitabine cisplatin (XP) chemotherapy with EBRT and 67 (72.8%) received XP chemotherapy. Patients in the XP-RT group received a mean 44.7 Gy of RT and a mean 5.6 cycles of XP chemotherapy, whereas patients in the XP group received a mean 4.0 cycles. The disease control rate was higher in the XP-RT group than in the XP group, but the difference was not statistically significant (56.0% vs. 41.5%, $p = 0.217$). Although neutropenia was significantly more frequent in the XP-RT than in the XP group (48% vs. 9%, $p < 0.001$), the rates of other toxicities and grade 3 and 4 toxicities did not differ. At a median follow-up of 5.3 months, PFS (4.3 vs. 1.9 months, $p = 0.001$) and OS (9.3 vs. 6.2 months, $p = 0.048$) were significantly longer in the XP-RT than in the XP group.

2.5. Stereotactic Body Radiotherapy (SBRT) in the Management of BTC

Technical advances over the past few years have enabled delivery of more precise, highly conformal radiation treatment to a tumour, maximally sparing adjacent normal tissues. This enhanced capability to spare normal tissues permits the safe delivery of a single or limited number of high dose radiation fractions to a target, whereas previously, small fractions of daily radiation were typically used to spare normal tissues. SBRT represents such an advance in RT delivery. It involves the delivery of very high doses of highly conformal radiotherapy in few fractions. Table 2-A summarises the SBRT studies published to date. These data suggest that SBRT may provide greater local control compared to standard fractionated RT. The treatment has been reported to be well tolerated. However, serious GI toxicity such as radiation-induced liver disease, bowel injury (duodenal perforation) is described in a small number of patients.

Table 2-A: Summary of published studies of SBRT for cholangiocarcinoma

Reference	Year	Patients (n)	Total Dose (Gy)	#	12-mth LC (%)	Median OS (months)	Comments
Herfarth[18] et al.	2001	3	14 - 26	1	71	NR	Target volume covered by 80% isodose
Tse [19]et al.	2008	10	32.5	6	65	15	Hypofractionated stereotactic RT
Goodman[20] et al.	2010	5	18 - 30	1	77	29	Single-fraction dose escalation study
Kopek [21]et al	2010	27	45	3	NR	11	22% rate of serious GI injury
Polistina[22] et al	2011	10	30	3	NR	36	All patients received concurrent Gemcitabine
Barney[23] et al	2012	10	55	5	100	14	Includes both recurrent and metastatic lesions
Ibara et al [24]	2012	11	30 (22-50)	1-10	50	11	Data from 4 academic centres in the US

Abbreviations: LC- Local control, NR- Not reported, GI- Gastrointestinal; # -fractions

Larger inoperable cholangiocarcinoma could benefit from local treatment as it would reduce symptoms such as pain and biliary obstruction followed by liver failure and death. Consolidation radiotherapy would be beneficial for these patients and several older reported studies have shown improvements in symptoms and survival [25-27].

Pollom et al [28] evaluated the impact of radiotherapy on survival in elderly patients using the SEER-Medicare database. Patients in the SEER-Medicare database with inoperable biliary tract tumours diagnosed between 1998 and 2011 were included. Of the 2343 patients included, 451 (19%) received radiotherapy within 4 months of diagnosis. In patients who received chemotherapy (n = 1053), receipt of radiation was associated with improved survival, with an adjusted hazard ratio of 0.82 (95% 0.70–0.97, P = 0.02). In patients who did not receive chemotherapy (n = 1290), receipt of radiation was not associated with improved survival, with an adjusted hazard ratio of 1.09 (95% 0.91–1.30, P = 0.34).

Extreme hypofractionation to lesions larger than 6 cm poses significant risk of severe toxicity (liver failure, bile duct stricture, gastro-intestinal tract perforations). An adjustment of single fraction dose and total dose approach could permit for delivery of tumoricidal doses of radiation with clinically acceptable toxicity when all other technical principles of SBRT delivery are maintained [29]. We have outlined below the evidence for larger intrahepatic lesions treated with hypofractionated radiotherapy.

Initial reports of moderate hypofractionation: In a phase 2 study that enrolled 128 patients with intrahepatic malignancies, including 46 patients with cholangiocarcinoma, patients received a median dose of 60.75 Gy delivered in 1.5-Gy, twice-daily fractions using a 3- dimensional conformal technique with concurrent hepatic artery floxuridine; improved survival over historical controls was noted, with 12 of 33 evaluable patients with cholangiocarcinoma demonstrating a complete or partial response [30].

In a recent series, Tao et al [31] report a retrospective analysis of 79 patients, and the impact of radiation dose on outcomes for inoperable, locally advanced intrahepatic cholangiocarcinoma. Patients treated to higher than the median radiation dose (biologic equivalent dose >80.5 Gy, equivalent to approximately >58 Gy in 15 fractions) achieved remarkable levels of long-term local control, overall survival, and progression-free survival (78%, 58%, and 39%, respectively, at 3 years) with a surprisingly low incidence of toxicities. Of note, biologic equivalent dose was the only variable statistically associated with outcomes on multivariable analysis. The outcomes of these patients [31] are within reported outcomes of patients with intrahepatic cholangiocarcinoma in surgical series. High dose hypofractionated protons [32] were tested in a phase II trial; of the 83 evaluable patients 39 had intrahepatic cholangiocarcinoma (ICC), of which 61% had prior treatment. The median tumour size was 6.0 cm (range, 2.2 to 10.9 cm) with 12.8% patients having multiple tumours. The median dose delivered was 58Gy and with a median follow-up among survivors of 19.5 months, the LC rate at 2 years was 94.1% for ICC. The median PFS rate was 8.4 months (95% CI, 5.0 to 15.7 months). All those who progressed locally had received <60 GyE. The median OS was 22.5 months (95% CI, 12.4 to 49.7 months), with 1-year and 2-year OS rates of 69.7% and 46.5%, respectively form start of radiotherapy. In terms of toxicity there were no grade 4 and 5 toxicities reported and 3 of the 39 ICC patients developed grade 3 radiation related toxicities: liver failure and ascites, stomach ulcer and elevated bilirubin. The authors conclude that high-dose, hypofractionated proton beam therapy is safe and associated with high rates of LC and survival for both HCC and ICC.

These data support the use of hypofractionated high dose radiotherapy in cholangiocarcinoma that are not suitable for SBRT and a strong rationale for comparison of chemotherapy with or without radiation. The use of SBRT techniques will permit the highest dose proposed to be achieved, whilst reducing the risk of toxicity. The high dose regimen (67.5 Gy in 15 fractions) is now the reference regimen in NRG-GI001 https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1320 a randomised (2:1) phase III study comparing the addition of radiotherapy (after cycle 3) to standard of care CisGem alone in patients with unresectable, locally advanced IHC.

2.6. Rationale for Use of SBRT after Systemic Treatment

2.6.1. Patterns of relapse following surgery

Following surgical resection, the most common pattern of relapse is local recurrence [33-35]. A review [36] of the patients with intrahepatic cholangiocarcinoma treated at Memorial Sloane Kettering between 1990-2006 has revealed that, after resection (possible in 82/270 patients), the median disease-specific survival was 36 months; recurrence was observed in 62.2% of patients at a median follow-up of 26 months, with the liver remnant involved most frequently (62.7%). The typical patterns of failure after resection were studied in 177 of patients with gallbladder (GBCA; n=97) and hilar cholangiocarcinoma (HCCA; n=80). Of those who developed disease recurrence, isolated locoregional disease was the first site of failure in 15% of patients with GBCA (who tended to relapse with metastatic disease) compared with 59% of patients with HCCA ($p<0.001$). On multivariate analysis initial disease site was an independent predictor of recurrence; this suggests different clinical behaviour and supports the rationale for a local approach for HCCA [10].

2.6.2. Evidence regarding radiosensitivity in cholangiocarcinoma

A multicentre retrospective study [37] of 12 large volume transplant centres in the US analysed 287 patients treated with external beam radiation (99%) with most also having received sensitizing chemotherapy (98%), brachytherapy (75%) and/or maintenance chemotherapy (65%); 214 patients had orthotopic liver transplantation. The average size of tumour as measured on CT in the 158 patients with a visible mass on cross sectional imaging was 2.7 cm (range 0.6-6.2 cm). Thirty-nine (~25%) patients had lesions larger than 3 cm. The median external beam radiation dose was 45 Gy (range 21-60 Gy) and median brachytherapy dose boost delivered afterwards was 20 Gy (range 9.8-60 Gy). At analysis of the explant, there was no tumour seen in 54% of the patients as a result of complete radiation-induced necrosis. Recurrence-free survival for patients who had received brachytherapy was similar to those who did not (HR, 1.05; 95% CI, 0.60 –1.85).

2.6.3. Progression after chemotherapy in locally advanced disease only

Most chemotherapy studies include both locally advanced and metastatic disease. As mentioned previously, in the ABC-02 study SD or PR was the best response for 39/44 patients with locally advanced disease in the CisGem arm. This suggests that a high number of patients continue to have localised disease that would benefit from local treatment. Unfortunately, it is not possible to extract the outcomes of patients with locally advanced disease in terms of relapse patterns from the ABC-02 study and the recently completed ABC-03 study has no mature results yet. ABC-03 (Randomised phase II trial of Cediranib (AZD2171) vs. placebo in addition to cisplatin/gemcitabine chemotherapy for patients with advanced biliary tract cancers) investigates the addition of Cediranib, a multi VEGF receptor tyrosine kinase inhibitor, in patients with locally advanced cholangiocarcinoma.

These data provide the rationale for exploring RT-based regimens as an additional treatment for inoperable locally advanced BTC. Despite the use of combined modality approaches the overwhelming majority of locally advanced cholangiocarcinoma patients will relapse and die of their disease. While standard fractionation radiation approaches may improve local control rates, local failure remains common despite contemporary approaches and dose escalation techniques. The currently available published data consists of heterogeneous phase I/II studies and outcomes such as OS are difficult to estimate, as other treatments (such as chemotherapy) are not always reported.

SBRT offers a higher possibility of local control compared to standard RT techniques, and is associated with fewer acute side effects. Another important advantage of SBRT is the short time required for this therapy (usually 1-2 weeks) compared with standard fractionated RT (5-6 weeks).

2.7. ABC-07 Overview

The purpose of the ABC-07 trial is examine whether adding SBRT to chemotherapy improves outcomes in patients with locally advanced, inoperable, biliary tract cancer. Initially we plan to undertake a feasibility phase (feasibility of patient recruitment and safety); as part of a randomised phase II study. Patients recruited during this feasibility stage will be included in the analysis of the full randomised phase II study (evaluating the relative merits of adding SBRT to CisGem combination in terms of PFS).

3. TRIAL DESIGN

This is a multicentre feasibility and phase II trial with 2:1 randomisation comparing cisplatin and gemcitabine (CisGem) chemotherapy + SBRT to CisGem chemotherapy alone, respectively.

If it is feasible to recruit 1 patient on average per month once 6 sites are open, the trial would continue into the full phase II trial. Patients recruited during the feasibility stage would be included in the analysis of the randomised phase II trial.

3.1. Trial Objectives

3.1.1. Primary objectives

Feasibility

- Is it feasible to deliver SBRT in a multicentre trial setting in a rare disease? In particular, will clinicians recruit to the trial and will sufficient patients accept randomisation?

Phase II

- To compare the efficacy of 6 cycles of CisGem followed by SBRT versus 8 cycles of CisGem.

3.1.2. Secondary objectives

- To compare the progression-free survival (PFS) at 9 months from randomisation between the two arms.
- To compare the frequency and severity of toxicities between the two arms.
- To assess the efficacy of CisGem + SBRT in relation to CisGem in terms of RR, PFS and OS.
- To assess the potential for CisGem + SBRT to downstage inoperable disease to operable disease.
- To examine Quality of Life (QoL) in the two treatment groups.

3.2. Trial Endpoints

3.2.1. Primary endpoints

Feasibility

- An average recruitment rate of at least 1 patient per month once 6 sites have been activated

Phase II

- To compare SBRT after CisGem to CisGem alone in terms of progression free survival (PFS) versus 8 cycles of CisGem

3.2.2. Secondary endpoints

- PFS rate at 9 months after randomisation
- Worst grade of AE (CTCAE v4.03)
- Best overall response (RECIST v1.1)
- PFS
- Duration of response
- OS

- Pattern of treatment failure
- Time to treatment failure
- Achieving downstaging permitting surgery
- QoL

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee (REC) approval
- Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA)
- **'**Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol 'site' refers to a hospital or other establishment or facility where trial activities are conducted.

All research sites must be able to comply with:

- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use (clinical trials) Act (SI 2004/1031) and all amendments.
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 [Timelines for Data Return].
- Monitoring requirements, as outlined in the protocol (Section 14 [Trial Monitoring and Oversight]) and the trial monitoring plan.
- If patients are being referred between trial sites then contractual arrangements must be in place between trial sites to cover all arrangements including insurance provision and financial issues. These arrangements must be in place prior to site activation.

In addition to the above:

- Recruiting sites must be able to comply with:
  - Clinical care and trial screening requirements as per protocol (see section 9.1 [Pre-registration]).
- Chemotherapy sites must be able to comply with:
  - Chemotherapy treatment schedules, clinical care, imaging, biological samples collection, processing and storage requirements as per protocol (see sections 8 [Trial Treatment], 9 [Assessments] and 10 [Exploratory Biological Studies]).
  - Central imaging review (see sections 17.2 Central review of imaging)
- SBRT sites must be able to comply with:
  - Radiotherapy QA processes, SBRT requirements as per protocol, imaging, clinical care and biological samples collection, processing and storage requirements (see sections 1.1 [Summary of Trial Design], 8.6 [Management of Adverse Events during SBRT], 9 [Assessments], 10 [Exploratory Biological Studies], 17.1 [Quality Assurance for SBRT] and Appendix IV [Radiotherapy]).
  - Central imaging review (see sections 17.2 Central review of imaging)
- Follow up sites must be able to comply with:
  - Clinical care, imaging and follow up schedules as per protocol (see section 9.6 [Assessments during follow up]). Biological samples collection, processing and storage requirements (see section 10 [Exploratory Biological Studies]).

4.1.1. Patient Identification Centres (PIC)

A PIC is a site where participants are identified and referred to an ABC-07 trial site **specifically to take part in the ABC-07 trial** (see section 4.1 [Site Selection] for definition of site within the ABC-07 trial). The trial site will be responsible for the subsequent assessment of potential participants, and taking informed consent to enter the participant into the study.

PIC sites do nothing more than identify participants and refer on. If a site is involved in anything further (taking consent, passing on research data, follow-up of patients) then they would be formally classed as a trial site and would need to apply for full R&D permissions to undertake the research (see section 4.1 [Site Selection]).

The research team at the trial site should involve the PIC site in the trial set up process. They should also liaise with some of the potential sites acting as a PIC site to discuss the details of the study, especially the inclusion and exclusion criteria in advance of setting a recruitment target and keep in regular contact. The PIC site should not provide the patient with any written information unless it has been ethically approved.

4.1.2. Selection of Principal Investigator and other investigators at sites

Sites must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site and ethics committee and regulatory authority, to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating biliary tract cancer, and expertise in upper GI SBRT if involved in the delivery of this treatment. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented as required. If a PI leaves or goes on a leave of absence for over 2 months, UCL CTC must be informed promptly and a new PI identified and appointed by the site.

4.1.3. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current signed and dated copy of the CV with documented GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site Initiation and Activation

Please note if your site will recruit patients who will be referred to another site(s) where trial activities will take place then your site will not be activated until all sites in the patient's trial pathway have been activated.

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead, radiotherapy team and site research team must attend, as appropriate for the site's role in the trial. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by site visit or teleconference with site. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient, as per monitoring plan.

4.2.2. Required documentation

The following documentation must be received by UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff).

- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately).
- A signed and dated copy of the PI's current CV (with documented up to date GCP training, or copy of GCP certificate).
- Relevant institutional approvals.
- Trial specific prescriptions.
- Radiotherapy QA approval (see section 17.1 [Quality Assurance for SBRT]).
- Assurance in writing that appropriate contractual provisions are in place with other trial sites as required (see also sections 4.1 [Site Selection] and 7.1 [Registration]).

In addition, the following agreements must be in place:

- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board).

4.2.3. Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI. **Sites must not approach any potential patients until they have received an activation letter from UCL CTC.**

4.2.4. PI responsibilities

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol.
- All relevant site staff are trained in the protocol requirements.
- Medical care of patients in the trial appropriate to their role in the trial.
- For recruiting sites, recruitment of appropriate patients.
- Timely completion and return of CRFs (including assessment of all adverse events).
- Prompt notification and assessment of all serious adverse events.
- That the site has facilities to provide **24 hour medical advice** for trial patients.

5. INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

All efforts will be made to enter all eligible patients into the trial. If local interpreters are not available at the site and fully informed consent is not deemed possible, the patient would not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient in the following days to confirm that they are still willing to participate in the trial. Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for ensuring:

- That the current approved version of the patient information sheet and consent form are used.
- That information on the consent form is complete and legible.
- That the patient has initialled all relevant sections and signed and dated the consent form.
- That an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient.
- That an appropriate member of staff make dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.).

Following registration, site staff should:

- Add the patient's trial number to all copies of the consent form. The original and 1 copy of the consent form need to be kept in the patient's medical notes and the investigator site file.
- Give the patient a copy of their signed consent form, patient information sheet, patient diary and patient contact card.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 [Withdrawal of Patients].

6. SELECTION OF PATIENTS AND DONORS

6.1. Screening Log

A screening log must be maintained by all recruiting sites and kept in the Investigator Site File. Recruiting sites should record all patients presenting with inoperable locally advanced biliary tract cancer at the site even if they were not given information about the trial. For patients who do not subsequently enter the trial, record the reason(s) why they were not entered. The log must be sent to UCL CTC when requested.

6.2. Patient Eligibility - Registration

There will be no exceptions to the eligibility criteria.

Queries in relation to the eligibility criteria must be addressed prior to registration. Patients are eligible for the trial if all the inclusion criteria are met, and none of the exclusion criteria applies.

Each patient's eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation that all eligibility criteria have been met must be documented in the patient's notes.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-registration assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1. Inclusion criteria

1. A histopathological/cytological diagnosis of locally advanced, non-resectable biliary tract carcinoma (intra- or extra-hepatic), (excluding cancer of the gall bladder and ampullary carcinoma)
2. Not suitable for radical surgery, or medically unfit for surgery as decided by a hepatobiliary MDT
3. Tumour visible on cross-sectional imaging and suitable for targeting with SBRT.
4. Measurable disease (according to RECIST criteria v1.1). (If disease is not measurable using RECIST v1.1, due to location in the vicinity of the hilum, the tumour must be visible for targeting with radiation using other multimodality imaging such as ERCP, MRCP).
5. Tumour (and nodes if involved) must be ≤12 cm in the longest dimension. For patients with non-measurable disease, sites should use the CT reconstructions (coronal or sagittal views) to measure tumour size.
6. Adequate biliary drainage
7. WHO PS 0 or 1
8. Adequate haematological function:
    - Haemoglobin ≥ 100 g/L (the use of transfusion to achieve desired Hb is acceptable)
    - White blood cell count (WBC) ≥ 3.0 x 10^9/L
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
9. Adequate liver function:
    - Total bilirubin ≤3.0 x ULN.Total bilirubin levels must be considered stable by the treating clinician e.g. more than one reading is required to show they are stable. Exceptions are possible for patients with known documented cases of Gilbert's syndrome, as long as the Bilirubin is stable and the treating clinician feels that the increased bilirubin is not due to obstruction or cholangitis.
    - ALT and/or AST ≤ 2.5 x ULN
    - ALP ≤ 5 x ULN

- Albumin > 25 g/L

10. Adequate renal function:
    - Serum urea < 1.5 x ULN
    - Serum creatinine < 1.5 x ULN
    - GFR ≥ 45 mL/min using a validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula). If the calculated creatinine clearance is less than 45 mL/min, GFR should be assessed using an isotopic clearance method to confirm GFR ≥ 45 mL/min. Alternatively, if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine to confirm GFR ≥ 45 mL/min .
11. Life expectancy >12 weeks
12. 16 years of age or over
13. Patients may have had prior chemotherapy as long as patient meets all other inclusion/exclusion criteria.
14. Patient must have given written informed consent

6.2.2. Exclusion criteria

1. Metastatic disease
2. Direct tumour extension in the duodenum, stomach, small bowel or large bowel.
3. Previous abdominal radiotherapy or previous selective internal radiotherapy such as hepatic arterial Yttrium therapy
4. Previous hypersensitivity to platinum salts
5. Any evidence of severe or uncontrolled systemic diseases which, in the view of the investigator, makes it undesirable for the patient to participate in the trial (including diabetes with established sensory peripheral neuropathy, unstable or uncompensated respiratory, cardiac, hepatic or renal disease)
6. Patients who have a concurrent malignancy that is clinically unstable and requires tumour-directed treatment are not eligible. Exceptions include low grade malignancies that do not require active treatment, such as early prostate cancer under surveillance or chronic lymphocytic leukaemia.
7. History of prior malignancy that could interfere with the response evaluation or survival. Exceptions include:
    - in-situ carcinoma of the cervix treated by cone-biopsy/resection,
    - non-metastatic basal and/or squamous cell carcinomas of the skin,
    - any early stage malignancy diagnosed over two years ago and radically treated.
8. Other concomitant anti-cancer therapy (except steroids)
9. Any psychiatric or other disorder likely to impact on informed consent
10. Women who are pregnant or breast-feeding

NB. Whilst not excluded, patients with **significant** hearing impairment must be made aware of potential ototoxicity and may choose not to be included. If included, it is recommended that audiograms be carried out at baseline and prior to cycle 2 of CisGem.

6.3. Patient Eligibility - Randomisation

Patients should be randomised during week 1 of cycle 5 of CisGem, once the results of the cycle 4 scans are available. In exceptional circumstances patients may be randomised during week 2 of cycle 5 following discussion with UCL CTC.

There will be no exceptions to the eligibility criteria.

Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Each patient's eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation that all eligibility have been met must be documented in the patient's notes.

6.3.1. Inclusion criteria

- Patients must be considered by the Investigator to be fit to receive either SBRT or to complete 8 cycles of CisGem as described in this protocol at the time of randomisation.
- Patients must have partial response (PR), stable disease (SD) or complete response (CR) according to RECIST v1.1 if measurable disease, or CR or non-CR/non-progressive disease if non-measurable disease, on the end of cycle 4 imaging.

6.3.2. Exclusion criteria

- Patients who have objective disease progression after cycle 4 of CisGem.

6.4. Pregnancy and birth control

6.4.1. Definition of women of childbearing potential (WOCBP) and fertile men

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 12 consecutive months (i.e. postmenopausal means the woman has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- had premature ovarian failure confirmed by a specialist gynaecologist

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

6.4.2. Risk of exposure to trial treatment during pregnancy

The risk of exposure to chemotherapy has been evaluated using the safety information available in Cisplatin and Gemcitabine SPCs. The risk of exposure to radiotherapy has been evaluated by the Trial Management Group with reference to information provided on the CRUK website (http://www.cancerresearchuk.org/).

The chemotherapy has been assessed as having a high risk of teratogenicity/fetotoxicity and genotoxicity. There are no adequate data from the use of gemcitabine in pregnant patients. Studies in animals have shown reproductive toxicity and therefore gemcitabine must not be used during pregnancy. Cisplatin may also be toxic to the foetus when administered to a pregnant woman.

It is unlikely that radiotherapy to the upper part of the abdomen in premenopausal women causes the menopause, as the uterus or ovaries will not be directly in the radiotherapy fields. There is, however, a risk of damage due to scattered radiation. Radiotherapy usually doesn't affect a man's ability to father children, however, sperm produced after treatment may still be fertile but could be damaged. The external radiotherapy has been assessed as having a possible risk of human genotoxicity/teratogenicity/fetotoxicity.

Overall, trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity and genotoxicity.

6.4.3. Pregnancy testing

All female participants who are WOCBP must have a pregnancy test within 7 days of registration and starting chemotherapy. Pregnancy testing must be repeated within 7 days prior to starting SBRT for WOCBP randomised to receive radiotherapy.

6.4.4. Contraceptive advice

Requirement for female patients:

All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from informed consent and until 6 months post last chemotherapy administration, or 12 months post last radiotherapy administration (if randomised to receive SBRT). Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral (e.g. desogestrel)
  - injectable
  - implantable[1]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1,2]
- sexual abstinence[3]

1. Contraception methods that are considered to have low user dependency.
2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
3. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Requirement for male patients with female partners who are pregnant or WOCBP:

Due to the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including male patients who have had vasectomies) must consent to use condoms with female partners who are WOCBP or partners who are pregnant, during treatment and until 6 months post last chemotherapy administration, or until 12 months post last radiotherapy administration (if randomised to receive SBRT).
- **Male patients must also advise their female partners who are WOCBP regarding contraceptive requirements as listed above for female patients who are WOCBP.**

For female and male patients:

The method(s) of contraception used must be stated in the patient medical notes. **The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.**

6.4.5. Action to be taken in the event of pregnancy

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 12 [Pharmacovigilance] for details on the reporting procedure). Trial treatment is strictly contraindicated in pregnant or breast-feeding women.

Female patients:

If a female patient becomes pregnant:

- prior to initiating treatment, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice).
- during treatment, the patient will be withdrawn from further treatment and, if they consent to pregnancy monitoring, followed up until pregnancy outcome.
- after the end of the treatment, but during the pregnancy at-risk period**,** the patient will be followed up until pregnancy outcome if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant between the patient's informed consent and 6 months after the end of chemotherapy or 12 months after the end of radiotherapy (for patients randomised to receive SBRT), the male participant can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

Lactation

Cisplatin is excreted in breast milk. Patients treated with cisplatin must not breastfeed.

It is not known whether gemcitabine is excreted in human milk and adverse events on the suckling child cannot be excluded. Breast-feeding must be discontinued during gemcitabine therapy.

Long term infertility

Since treatment with cisplatin and gemcitabine may cause irreversible infertility, it is recommended that men who wish to become fathers in the future are provided with advice regarding cryoconservation of their sperm prior to starting treatment.

Genetic consultation is recommended for patients receiving treatment with cisplatin who wish to have children after ending their treatment.

Radiotherapy to upper abdomen (liver) is unlikely to cause immediate amenorrhea; however, patients should be counselled that they may be at risk for early menopause. Patients may want to consider fertility preservation before or after treatment.

7. REGISTRATION AND RANDOMISATION PROCEDURES

Patients will be registered into the trial to start treatment with CisGem. All patients will be scheduled to receive 6 cycles of CisGem. Patient registration must be performed prior to commencement of any trial treatment and trial treatment should start within 28 days of patient registration.

Once the results of the cycle 4 scans are available, patients eligible for randomisation will be randomised during week 1 of cycle 5 to receive either SBRT or another 2 cycles of CisGem, after completing cycle 6. In exceptional circumstances patients may be randomised during week 2 of cycle 5 following discussion with UCL CTC.

Both registration and randomisation will be undertaken centrally at UCL CTC.

REGISTRATION/RANDOMISATION CONTACT DETAILS
ABC-07 Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
General Queries: 020 7679 9608
Registration/Randomisation Fax Number: 020 7679 9871
Office hours: 9am to 5pm, Monday to Friday (excluding bank holidays)

7.1. Registration

It is important that the registering site is aware of all sites where trial activities will take place for each patient and that all such sites have been activated within the ABC-07 trial. This information will be required in order to register the patient (see also section 4 [Selection of Sites and Site Investigators]).

Trial-activities are:

- Recruitment
- Consent
- Administration of chemotherapy
- Planning and delivery of SBRT
- Collection, storage and shipping of biological samples for exploratory research
- Follow up
- Completion of case report forms

Following pre-registration evaluations (as detailed in section 9.1 [Pre-registration]), confirmation of eligibility and consent of a patient at a site, the registration form must be fully completed and faxed to UCL CTC. This will be used to confirm patient eligibility at UCL CTC. If further information is required UCL CTC will contact the person requesting registration to discuss the patient and may request updated forms to be faxed.

UCL CTC will e-mail confirmation of the patient's inclusion in the trial and their trial number to the main contact and pharmacy. The site should add the trial number to the registration form and consent form.

Please contact UCL CTC if the registration confirmation or a request for further information has not been received within 2 hours after faxing the forms.

Once a patient has been registered onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet.
- A patient diary. Patients should be asked to use this to record any adverse events up until 6 months post last chemotherapy administration. They must be reminded to bring this with them every time they visit the hospital for a trial assessment.
- A patient contact card. Site contact details for 24 hour medical care must be added to this card. Patients should be advised to carry this with them at all times while participating in the trial.

7.2. Randomisation

Following 6 cycles of CisGem, patients who have neither progressed nor stopped chemotherapy for any other reason will go on to receive either SBRT or 2 more cycles of CisGem (8 cycles in total). The randomisation to SBRT or 2 more cycles of CisGem will be in a 2:1 ratio.

Patients should be randomised during week 1 of cycle 5, as soon as the results of the cycle 4 imaging are available. In exceptional circumstances patients may be randomised during week 2 of cycle 5 following discussion with UCL CTC. The randomisation form must be fully completed and faxed to UCL CTC.

Patients will be stratified according to the following information:

- WHO Performance Status at baseline: 0 or 1
- Maximum tumour dimension (prior to starting CisGem): ≤ 6cm or > 6cm
- Prior therapy: Surgery or no surgery
- Disease site: Intrahepatic cholangiocarcinoma or other

UCL CTC will e-mail confirmation of the patient's treatment allocation to the main contacts at the randomising site and radiotherapy site (if different), and pharmacy. The site should add the treatment allocation to the randomisation form and send it to UCL CTC by post.

Please contact UCL CTC if the randomisation confirmation or a request for further information has not been received within 2 hours after faxing the forms.

Patients randomised onto the SBRT arm of the trial must be provided with a SBRT patient diary and should be asked to use this to record any adverse events. They must be reminded to bring this with them every time they visit the hospital for a trial assessment up until 6 months post last radiotherapy administration. Any adverse events recorded in the diary should be reviewed with the patient and documented in the patient's medical notes as appropriate. The patient diaries should be kept with the patient's CRF at site.

8. TRIAL TREATMENT

8.1. Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMPs are:

- Gemcitabine
- Cisplatin

8.1.1. Gemcitabine

Gemcitabine is currently licensed for use for cancer treatment in the UK. Gemcitabine will be sourced from routine hospital stock and its handling and management will be subject to standard procedures of the pharmacy. It will be administered to patients intravenously at a trial site. There is no specific brand of gemcitabine that must be used for this trial. Sites must ensure the active substance used is gemcitabine hydrochloride.

8.1.2. Cisplatin

Cisplatin is currently licensed for use for cancer treatment in the UK. Cisplatin will be sourced from routine hospital stock and its handling and management will be subject to standard procedures of the pharmacy. It will be administered to patients intravenously at a trial site. There is no specific brand of cisplatin that must be used for this trial. Sites must ensure the active substance used is cisplatin.

8.2. Treatment Summary

All patients will receive:

- 6 cycles of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 (CisGem) given intravenously on days 1 and 8 of a 21-day cycle.

Patients with stable disease or better on cycle 4 imaging will be randomised (2:1) during cycle 5 to receive:

- 5 or 15 fractions of stereotactic body radiation therapy (SBRT) given over 5-21 days (number of fractions and duration of therapy depends on the size of the tumour as measured on the end of cycle 4 imaging scan).

Or

- 2 more cycles of CisGem (for a total of 8 cycles).

SBRT should start no more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy.

For lesions ≤6cm: SBRT will be delivered in 5 fractions. The total dose prescribed may be 50, 45 or 40 Gy based on normal tissue constraints. The time between fractions should be 24 to 72 hours (preferred interval of 48 hours). The total duration of SBRT treatment should not exceed 21 days.

For lesions > 6cm: SBRT will be delivered in 15 consecutive daily fractions, delivered on weekdays over 19-21 days. Total dose prescribed may be 45, 58.1 or 67.5Gy based on normal tissue constraints. The total duration of SBRT treatment should not exceed 34 days.

All treatment will be discontinued for patients who have objective disease progression on the cycle 4 imaging.

For more information on the randomisation process see section 7.2 [Randomisation].

8.3. Trial Treatment - CisGem

8.3.1. CisGem pre-treatment

Hydration schedule for cisplatin

The hydration and electrolyte regimen (KCl +/- $MgSO_4$) for cisplatin administration will be determined by locally agreed pharmacy procedures and guidelines. The following regimen is recommended:

- KCl 20 mmol and $MgSO_4$ 8 mmol during the cisplatin infusion followed by 500 mL 0.9% NaCl solution prior to the gemcitabine.

However, alternative local regimens are acceptable.

Anti-emetics

Anti-emetics should be given according to local practice.

8.3.2. Administration of CisGem

All patients will be scheduled to receive 6 cycles of combination chemotherapy with cisplatin and gemcitabine. Patients randomised to receive CisGem only, will be scheduled to receive 2 more cycles of CisGem, for a total of 8 cycles. Cisplatin and gemcitabine will be given intravenously on days 1 and 8 of a 21-day cycle, in the following doses:

- **Cisplatin:** 25 mg/m^2, followed by;
- **Gemcitabine:** 1000 mg/m^2

Infusion times and volumes should be according to local policy.

Dose banding for cisplatin and gemcitabine may be used according to local policy. The CTC will request each site to state upfront whether or not dose banding will be used.

BSA should be calculated as per local practice. BSA should be recalculated in case of weight variation of greater than 10% from start of treatment.

8.4. Trial Treatment – SBRT

8.4.1. Administration of SBRT

All patients randomised to receive SBRT will be planned to receive 5 or 15 fractions of SBRT given over 5-21 days (number of fractions and duration of therapy depends on the size of the tumour as measured on the end of cycle 4 imaging scan).

SBRT should start not more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy. A contrast enhanced liver protocol CT must be obtained for treatment planning in custom immobilisation.

For lesions ≤6cm: SBRT will be delivered in 5 fractions. The total dose prescribed may be 50, 45 or 40 Gy based on normal tissue constraints. The time between fractions should be 24 to 72 hours (preferred interval of 48 hours). The total duration of SBRT treatment should not exceed 21 days.

For lesions > 6cm: SBRT will be delivered in 15 consecutive daily fractions, delivered on weekdays over 19-21 days. Total dose prescribed may be 45, 58.1 or 67.5Gy based on normal tissue constraints. The total duration of SBRT treatment should not exceed 34 days.

A linear accelerator with at least 6 MV should be used, capable of daily image guidance and IMRT delivery. On-line imaging prior to each fraction of radiotherapy is mandatory.

For full details on SBRT planning and delivery please see Appendix IV.

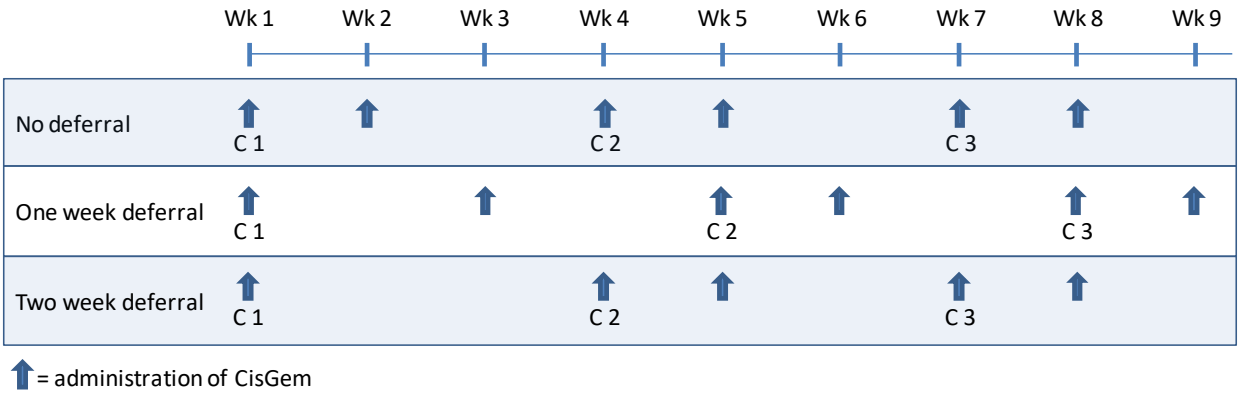
8.5 Management of Adverse Events during CisGem

8.5.1. Principles of adverse event management

The following general guidance should be followed for management of adverse events (AEs) and dose reductions.

1. AEs should be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).
2. Treat each AE with maximum supportive care (including withholding administration of the agent suspected of causing the adverse event where required). If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of trial medications along with appropriate continuing supportive care, except where this conflicts with guidance given elsewhere in this section 1.4.
3. For AEs which are considered by the Investigator unlikely to develop into serious or life-threatening events (e.g. alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption. Rationale for this should be clearly documented in the patient's notes.
4. No dose reductions or interruptions are required for anaemia (non-haemolytic) if it can be satisfactorily managed by transfusions or erythropoietin.
5. **Gemcitabine dose should only be reduced by 25%** (except for myelosuppresion which can then be further reduced by another 25% following discussion with UCL CTC). Otherwise, no additional reductions are permitted.
6. **Dose reductions are not permitted for cisplatin.**
7. Where several AEs with different grades or severity occur at the same time, the dose modifications applied should be the greatest reduction applicable.
8. If, in the opinion of the Investigator, an AE is considered to be due solely to one drug (e.g. renal toxicity associated with cisplatin administration) then it is only the dose of the responsible drug that needs to be reduced or interrupted unless this conflicts with the guidance given elsewhere in this section 8.5 (Trial Treatment – SBRT).
9. Cisplatin should never be administered on its own. If gemcitabine is not given, then cisplatin should not be given.
10. All omissions should be managed according to Figure 8-A: Management of treatment delays
11. All dose modifications should be documented with clear reasoning in the medical notes.
12. If chemotherapy is delayed for more than 3 weeks for an adverse reaction, the patient should be withdrawn from treatment.
13. Trial treatment is strictly contraindicated in pregnant or breast-feeding women.

Figure 8-A: Management of treatment delays



8.5.2. Management of haematological AEs

The recommendations in Table 8-A**:** Management of haematological AEs below for alteration in cisplatin and gemcitabine schedule are based on the day 1 and 8 blood counts. Dose alterations should follow the most conservative option in cases where there is a conflict.

If day 8 must be deferred by more than 1 week, then it should be omitted altogether and the next cycle should start once the patient's blood counts have recovered (refer to figure 8-A).

Table 8-A: **Management of haematological AEs during CisGem**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Gemcitabine	Cisplatin
≥ 1	and	≥ 100	No modification	No modification
0.5-0.9	or	50-99	Reduce by 25%[1]	No modification
< 0.5	or	< 50	Delay[2] until ANC ≥$1x10^9$/L and platelets ≥$100x10^9$/L. If day 8 is delayed > 1 week, omit it altogether.	Delay until next dose of gemcitabine can be administered.

[1] *Re-escalate the dose of gemcitabine to full dose upon recovery of haematological adverse event (AE) in order to maintain the dose-intensity of therapy. Dose may be reduced by a further 25% for myelosuppression only (for a total dose reduction of 50%) following discussion with the UCL CTC.*

[2] *If delay is > 3 weeks for haematological AE, the patient will be withdrawn from treatment.*

8.5.3. Management of renal AEs

Cisplatin should be administered only if adequate renal function can be demonstrated. If calculated creatinine clearance is <45 mL/min, use the more accurate isotope clearance method, ensuring the patient is adequately hydrated prior to this test, before further cisplatin administration. Proceed with cisplatin if the isotope clearance is ≥ 45 mL/min, otherwise omit cisplatin until recovery of renal function. If cisplatin has to be omitted, continue with gemcitabine dosing according to the full blood count. If a sudden increase in creatinine occurs, haemolytic uraemic syndrome should be ruled out.

For patients who required an isotope clearance test at screening to confirm adequate renal function, a repeat test (to confirm GFR ≥ 45 mL/min) is required only if there has been more than 10% increase in serum creatinine.

Table 8-B: **Management of renal AEs during CisGem**

GFR	Gemcitabine	Cisplatin
≥45 mL/min	No modification	No modification
<45 mL/min	No modification	Omit until GFR ≥45 mL/min

8.5.4. Management of nausea or vomiting

Nausea or vomiting should be managed with anti-emetics. Dose modifications should be considered only if nausea or vomiting cannot be adequately controlled with optimal treatment with anti-emetics.

Table 8-C: **Management of nausea or vomiting during CisGem**

Grade	Gemcitabine	Cisplatin
Grades 1 and 2	No modification	No modification
Grades 3 and 4	Delay until recovery to grade 0/1. If no improvement after omitting cisplatin, reduce gemcitabine by 25%*	Delay until recovery to grade 0/1 and omit cisplatin first from further treatment*
	Stop treatment if nausea or vomiting cannot be controlled with optimal anti-emetics and dose reduction	

**investigator discretion as to whether a particular non-haematological AE requires a dose reduction or treatment delay*

8.5.5. Management of fatigue

Table 8-D: **Management of fatigue during CisGem**

Grade	Gemcitabine	Cisplatin
Grades 1 and 2	No modification	No modification
Grades 3 and 4	Reduce by 25%*	No modification
	Stop treatment if fatigue does not responded to dose reduction	

**investigator discretion as to whether a particular non-haematological AE requires a dose reduction or treatment delay*

8.5.6. Management of oedema

Table 8-E: **Management of oedema during CisGem**

Grade	Gemcitabine	Cisplatin
Grades 1 and 2	No modification	No modification
	Give postural advice, consider appropriate diuretics	
Grades 3 and 4	Dipstick urine test for protein followed by 24-hour urinary protein estimation if result ≥+	
	Delay until recovery to baseline (with use of appropriate diuretics) then reduce gemcitabine by 25%*	Delay until recovery to baseline (with use of appropriate diuretics)*
	Stop treatment if oedema does not respond to dose modification and use of diuretics	

**investigator discretion as to whether a particular non-haematological AE requires a dose reduction or treatment delay*

8.5.7. Management of peripheral neuropathy

Table 8-F: **Management of peripheral neuropathy during CisGem**

Grade	Gemcitabine	Cisplatin
Grade 1 or transient peripheral neuropathy	No modification	No modification
Grade 2	No modification	Omit cisplatin until recovery to baseline, then continue at full dose. If no recovery, treat as for grade 3-4.
Grade 3 and 4	No modification	Stop permanently

8.5.8. Management of tinnitus

No dose modifications are required if there is a full recovery back to baseline levels between cycles. If no recovery between cycles omit cisplatin permanently and continue gemcitabine at full dose.

8.5.9. Management of pulmonary AEs

For grade 2-4 pulmonary AEs, supportive therapy (high dose steroids) should be initiated immediately. Treatment with CisGem should be permanently discontinued.

8.5.10. Management of biliary tract obstruction

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures should be undertaken to diagnose (e.g. by ultrasound and/or CT scan) and relieve the obstruction (e.g. by ERCP/PTC +/- stent insertion/drainage). Chemotherapy will be delayed until the LFTs have improved to the pre-treatment eligibility levels (see section 6.2.1 [Inclusion criteria]). Chemotherapy may then resume at the start of the next cycle of treatment.

In the event the biliary stent is not blocked or has been replaced, and bilirubin is high or decreasing to ≤3 xULN, however the patient is deemed fit to receive chemotherapy, then treatment can be delivered.

Biliary tract obstruction by itself shall not constitute evidence of disease progression. CT or MRI/MRCP imaging will be performed at the planned time points (i.e. after cycle 4 and completion of treatment). However, if there is radiological evidence of objective disease progression during the investigation of obstructive jaundice, treatment with CisGem shall be discontinued.

8.5.11. Management of other non-haematological AEs

No dose modifications for alopecia are required. Extravasations and allergic reactions should be managed as per local policy.

In case of other grade 3 or 4 clinically significant non-haematological AEs, it is at the investigator's discretion as to whether a particular non-haematological AE requires a dose reduction or treatment delay. The TMG are available to discuss the management of any grade 3 or 4 toxicity. If you would like to discuss the management of AEs with the TMG, please contact UCL CTC.

8.5.12. CisGem delays for reasons not related to AEs

In the event of a delay of up to 3 weeks to CisGem treatment for reasons other than AEs, treatment should continue. Resume treatment at day 1 of the next treatment cycle. For one week delays refer to **Figure 8-A: Management of treatment delays**. For delays lasting more than 3 weeks, contact UCL CTC for advice.

8.6. Management of Adverse Events during SBRT

SBRT should start not more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy.

8.6.1. Criteria for starting SBRT

Patients will be assessed before starting SBRT and the following criteria must be met:

- No grade 3 or 4 toxicity persisting from chemotherapy
- Total bilirubin ≤3.0 x ULN. Total bilirubin levels must be considered stable by the treating clinician e.g. more than one reading is required to show they are stable.
- Child Pugh score ≤ 7 (see Appendix II)
- Clinician confirms fitness to receive SBRT

8.6.2. Criteria for continuing SBRT

Patients will be assessed at least once during SBRT for AEs. SBRT will continue as planned as long as the following criteria are met:

- Total bilirubin ≤3.0 x ULN. Total bilirubin levels must be considered stable by the treating clinician e.g. more than one reading is required to show they are stable.
- Child Pugh score ≤ 7 (see Appendix II)
- Clinician confirms fitness to receive SBRT

8.6.3. Interruptions to SBRT

When an interruption to SBRT treatment occurs for any reason (e.g. due to AEs or bank holidays) the radiotherapy prescription remains unchanged (i.e. the dose prescribed remains as planned with the same number of fractions even if this is delivered over a longer treatment time). **Additional fractions should NOT be given on the same day**. Up to 3 consecutive treatment days are accepted as a break, but if SBRT is interrupted for more than 7 days in total due to ARs then treatment should be permanently discontinued.

- SBRT treatment for tumours ≤6cm (5 fractions) should be completed within a maximum of 21 days.
- SBRT treatment for tumours >6cm (15 fractions) should be delivered within a maximum of 34 days.

8.6.4. Management of haematological AEs

Table 8-G: **Management of haematological AEs during SBRT**

Grade		ART
Grade 1	ANC <LLN – 1.5 x 10^9/L	Continue
	Platelets <LLN - 75 x 10^9/L	Continue
Grade 2	ANC <1.5 - 1.0 x 10^9/L	Continue
	Platelets <75 -50 x 10^9/L	Continue
Grade 3	ANC <1.0 - 0.5 x 10^9/L	Withhold RT until grade ≤ 2, then restart Bloods should be repeated every 48 hours to reassess[1]
	Platelets <50 - 25 x 10^9/L	Withhold RT until grade ≤ 2, then restart Bloods should be repeated every 48 hours to reassess[1]
Grade 4	ANC <0.5 x 10^9 /L	Withhold RT for up to 1 week until grade ≤ 2 then restart Bloods should be repeated every 48 hours to reassess[1]
	Platelets < 25.0 x 10^9/L	Withhold RT for up to 1 week until grade ≤ 2 then restart Bloods should be repeated every 48 hours to reassess[1]

[1] *Bloods only need to be repeated every 48 hours while the patient is receiving SBRT.*

8.6.5. Management of diarrhoea

Treatment induced diarrhoea should be managed using anti-diarrhoea tablets such as loperamide.

Table 8-I: **Management of diarrhoea during SBRT**

Grade	SBRT
Grade 1 and 2	Continue
Grade 3 and 4	Withhold RT until grade ≤ 2 then resume

8.6.6. Management of nausea or vomiting

Table 8-J: **Management of nausea or vomiting during SBRT**

Grade	SBRT
Grade 1 and 2	Prophylactic antiemetic pre-RT and escalate as required, continue RT
Grade 3 and 4	Withhold RT until grade ≤ 2, then resume with antiemetic cover.

8.6.7. Management of deranged bilirubin

In case bilirubin rises to >3.0 x ULN, bloods should be repeated every 48 hours while the patient is receiving SBRT to reassess. If the level continues to rise, investigations to assess the biliary duct or stent patency should be initiated.

Table 8-K: **Management of bilirubin during SBRT**

Bilirubin	SBRT
≤ 3.0 x ULN	Continue
> 3.0 x ULN	Withhold RT until ≤ 3.0 x ULN, then resume Bloods should be repeated every 48 hours to reassess[1]

[1] *Bloods only need to be repeated every 48 hours while the patient is receiving SBRT.*

8.6.8. Management of deranged AST or ALT

In case AST or ALT rise to grade 3 or greater, bloods should be repeated every 48 hours while the patient is receiving SBRT to reassess.

Table 8-L: **Management of AST or ALT during SBRT**

Grade	SBRT
Grades 1 and 2	Continue
Grade 3 but AST or ALT<10x ULN	Continue
Grade 3 but AST or ALT>10x ULN	Withhold RT until grade ≤2 then resume Bloods should be repeated every 48 hours to reassess.[1]
Grade 4 AST or ALT	Withhold RT for 1 week and until grade ≤2, then resume Bloods should be repeated every 48 hours to reassess.[1]

[1] *Bloods only need to be repeated every 48 hours while the patient is receiving SBRT.*

8.6.9. Management of other AEs

Table 8-M below describes dose modifications in case of other non-haematological AEs which are considered to be related to SBRT.

Table 8-M: **Management of other AEs during SBRT**

Grade	SBRT
Grade 1 and 2	Continue RT
Grade 3	Withhold RT until grade ≤2 then restart
Grade 4	Discontinue RT (STOP PERMANENTLY)

8.7. Management of Overdoses, Trial Treatment Error and Occupational Exposure

8.7.1. Overdoses

An overdose is an administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as an overdose by the trial team at site or by the Sponsor upon review.

Overdoses should be reported on an incident report (see section 13.1). Any adverse events resulting from an overdose should be reported as an SAE (see section 12.2.5 for reporting procedures).

8.7.2. Cisplatin

Caution in administering cisplatin is essential in order to prevent an inadvertent overdose. An acute overdose in cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal. In the event of a suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy as necessary.

8.7.3. Gemcitabine

In the event of a suspected overdose with gemcitabine, the patient should be monitored with appropriate blood counts and should receive supportive therapy as necessary.

8.7.4. Radiotherapy

In the event of exposure to excess radiation this should be reported according to Ionising Radiation (Medical Exposure) (IRMER) Regulations, the patient should be closely monitored and any side effects managed as per local requirements/IRMER.

8.7.5. Trial treatment error

Any unintentional error in prescribing, dispensing, or administration of a trial treatment while in the control of a healthcare professional or patient. The error can be identified either by the trial team at site or by the Sponsor upon review.

Trial Treatment errors should be reported on in incident report (see section 13.1 Incident Reporting). Any adverse events resulting from a medication error should be reported as an SAE (see section 12.2.5 for reporting procedures).

8.7.6. Occupational exposure

Occupational exposure is any exposure to a trial treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1[Incident Reporting]).

8.8. Supportive Therapy

8.8.1. Supportive therapy during CisGem

Investigators should follow local guidelines. See sections 8.3.1 [CisGem pre-treatment] and 8.5 [Management of Adverse Events during CisGem Supportive therapy during SBRT].

Investigators should follow local guidelines. Antiemetics (e.g. dopamine receptor (D2)), antagonist (e.g. domperidone), or 5HT3 antagonists (e.g. ondansetron) should be considered to be used prior to each fraction to prevent nausea if the stomach is expected to receive any radiation. They may be used for symptomatic nausea or vomiting.

Treatment induced diarrhoea should be managed using anti-diarrhoea tablets such as loperamide.

H_2 blockers or proton pump inhibitors are strongly recommended if 20 Gy or more is delivered to the luminal gastrointestinal tract or at the treating clinician's discretion. The medications should be started before completion of RT and continued for at least 6 months.

Analgesics may be used to treat tumour or therapy induced pain. Recommendation is to avoid NSAIDS in order to reduce luminal GI tract irritation

8.9. Contraindications

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal products may potentiate the toxic effect of cisplatin. During treatment with cisplatin caution is advised with substances that are eliminated predominantly by renal excretion (e.g. cytostatic agents such as bleomycin and methotrexate) because of potentially reduced renal elimination.

Reduction of the blood's lithium values was noticed in a few cases after treatment with cisplatin combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium levels.

Concurrent administration of yellow fever vaccine with cisplatin or gemcitabine is contraindicated.

Patients may receive all concomitant therapy deemed to provide adequate supportive care at the investigator's discretion. However, the use of experimental drugs is not permitted until at least 28 days after completion of the last trial treatment. All medications or other treatments taken by the patients during the trial (including those initiated prior to the start of the trial) must be recorded in the patient's clinical notes.

8.10. Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

8.10.1. IMP accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including, dispensing, returned medication and destruction of returned medication. Accountability forms will be supplied, and must be used, unless there is prior agreement from UCL CTC for the pharmacy to use alternative in-house records.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 14.1 [Central Monitoring].

Refer to Summary of Drug Arrangements in the Pharmacy Site File for further details.

8.11. Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Subsequent treatment will be at the discretion of the treating clinician. The use of experimental drugs is not permitted until at least 28 days after completion of the last trial treatment (see section 8.9 [Contraindications]).

Also refer to section 15 [Withdrawal of Patients] for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9. ASSESSMENTS

9.1. Pre-registration

For summary schedule of assessments please see Appendix VI Schedule of Assessments.

Patients must give written informed consent before any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Histological or cytological confirmation of biliary tract cancer

Ideally within 28 days (and not more than 42 days) prior to registration:

- CT scan to include thorax/abdomen/pelvis
- For patients with measurable disease RECIST (v1.1) measurements must be taken
- MRI scan of liver is strongly recommended
- Please note: TNM version 8 should be used for the duration of the trial

Within 7 days prior to registration:

- Relevant medical history, including ongoing medication and documentation of baseline symptoms
- Physical examination
- Height and weight, vital signs (including pulse, blood pressure and temperature)
- WHO performance status (see Appendix III)
- Full blood count (FBC) + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- GFR estimated using a validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula). If calculated GFR is <45 mL/min, an isotope clearance test is required (Cr51-EDTA or 99mTc-DTPA). Alternatively, if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine.
- International Normalised Ratio (INR) (may be done prior to registration but not required. Must be done within 7 days prior to the start of treatment)
- Pregnancy test (for WOCBP)
- Audiogram, if applicable (recommended for patients with mildly impaired hearing or tinnitus)

9.2. Pre-treatment

The following pre-treatment assessments are required.

Within 14 days prior to the first dose of trial treatment:

- Quality of life (EQ5D and EORTC QLQ- BIL21)
- CA19-9
- Blood samples for exploratory research (see section 10 [Exploratory Biological Studies] for more information)

The following pre-registration assessments must be repeated if they were carried out >7 days prior to start of treatment, (patients should not start treatment unless all eligibility criteria remain fulfilled):

- Assessment and documentation of AEs
- Physical examination
- Weight and vital signs (including pulse, blood pressure and temperature)
- WHO performance status (see Appendix III)

- FBC + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- GFR estimated using a validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula). If calculated GFR is <45 mL/min, an isotope clearance test is required (Cr51-EDTA or 99mTc-DTPA). Alternatively, if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine. For patients who required an isotope clearance test at screening to confirm adequate renal function, a repeat test (to confirm GFR ≥ 45 mL/min) is required only if there has been more than 10% increase in serum creatinine.

- INR
- Pregnancy test (for WOCBP)

9.3. During CisGem

Chemotherapy should begin within 28 days of the patient being registered.

9.3.1. Day 1

For cycle 1 day 1, see section 9.2 (Pre-treatment).

For all subsequent cycles, the following should be carried out **within 3 days prior to day 1** CisGem administration:

- Physical examination
- Weight and vital signs (including pulse, blood pressure and temperature)
- Assessment and documentation of AEs
- WHO performance status (see Appendix III)
- FBC + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- GFR estimated using a validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula). If calculated GFR is <45 mL/min, an isotope clearance test is required (Cr51-EDTA or 99mTc-DTPA). Alternatively, if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine. For patients who required an isotope clearance test at screening to confirm adequate renal function, a repeat test (to confirm GFR ≥ 45 mL/min) is required only if there has been more than 10% increase in serum creatinine.
- CA19-9
- **Prior to cycle 2 only**: Audiogram, if applicable (recommended for patients with mildly impaired hearing or tinnitus)

Patients should be reminded to bring their diary with them to every trial visit up until 6 months post last chemotherapy administration. Any adverse events recorded in the diary should be reviewed with the patient and documented in the patient's medical notes as appropriate. The patient diaries should be kept with the patient's CRF at site.

9.3.2. Day 8

The following should be carried out **within 3 days prior to day 8** CisGem administration:

- Assessment and documentation of AEs
- WHO performance status (see Appendix III)
- FBC + differential

- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- GFR estimated using a validated creatinine clearance calculation (e.g. Cockcroft-Gault or Wright formula). If calculated GFR is <45 mL/min, an isotope clearance test is required (Cr51-EDTA or 99mTc-DTPA). Alternatively, if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine. For patients who required an isotope clearance test at screening to confirm adequate renal function, a repeat test (to confirm GFR $\geq$ 45 mL/min) is required only if there has been more than 10% increase in serum creatinine.

9.3.3. End of cycle 4

The following should be carried out prior to the end of cycle 4 and the results should be available for cycle 5:

- CT scan to include thorax/abdomen/pelvis (this scan can be performed from Cycle 4 Day 8 onwards)
- For patients with measurable disease RECIST (v1.1) measurements must be taken
- MRI scan of liver is strongly recommended

In addition to the above, the following should be carried out prior to starting cycle 5:

- Quality of life (EQ5D and EORTC QLQ- BIL21)
- Blood samples for exploratory research (see section 10 [Exploratory Biological Studies] for more information)

9.3.4. During cycle 5

Patients who have neither progressed nor stopped chemotherapy for any other reason should be randomised to receive either SBRT or 2 further cycles of CisGem following completion of 6 cycles of CisGem (for a total of 8 cycles). Patients should be randomised during week 1 of cycle 5, as soon as the results of the cycle 4 imaging are available. See also section 7.2 [Randomisation].

9.4. SBRT

SBRT should start not more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of CisGem chemotherapy.

9.4.1. Pre-SBRT assessments

The following assessments must be performed within 30 days (and no more than 37 days) prior to commencing SBRT and should be combined with hospital visits for cycle 6 assessments if timeline permits:

- Physical examination
- Vital signs (including pulse, blood pressure and temperature)
- Assessment and documentation of AEs
- WHO performance status (see Appendix III)
- Child-Pugh score (see Appendix II)
- FBC + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- INR
- CA19-9

Within 7 days prior to commencing SBRT:

- Pregnancy test (for WOCBP)

9.4.2. During SBRT

Patients will be assessed at least once during the 5 fractions regime and weekly during the 15 fractions regime, and the following must be performed:

- Physical examination
- Vital signs (including pulse, blood pressure and temperature)
- WHO performance status (see Appendix III)
- Child-Pugh score (see Appendix II)
- INR
- Assessment of AEs
- FBC + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH

9.5. Completion of Treatment

The following should be carried out between 28-35 days after the last fraction of SBRT or the last dose of CisGem for all patients (including patients who have progressed after 4 cycles):

- Physical examination
- Vital signs (including pulse, blood pressure and temperature)
- Assessment and documentation of AEs
- WHO performance status (see Appendix III)
- FBC + differential
- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH
- INR (SBRT patients only)
- CA19-9
- Quality of life (EQ5D and EORTC QLQ- BIL21)
- Blood sample for exploratory research (see section 10 [Exploratory Biological Studies] for more information)
- CT scan to include thorax/abdomen/pelvis to document disease status. (Not applicable if patient has progressed)
- For patients with measurable disease RECIST (v1.1) measurements must be taken
- MRI scan of liver is strongly recommended (Not applicable if patient has progressed

9.6. Assessments during follow up until disease progression

Patients should be followed up in clinic for up to two years after registration. All efforts should be made by the site to contact the patient's GP to assess their condition if a patient fails to attend a clinic or cannot be followed up at site.

The following should be carried out every 3 months +/- 4 weeks after the last fraction of SBRT or the last dose of CisGem:

- WHO performance status (see Appendix III)
- Assessment and documentation of AEs (*up to 6 month post last trial treatment*)
- FBC + differential (*3 and 6 month follow up visit only*)

- Serum biochemistry: sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT and LDH (3 and 6 month follow up visit only)
- INR *(SBRT patients at 3 month follow up visit only)*
- CA19-9 *(6, 12, and 18 month follow up visits only)*
- Quality of life (EQ5D and EORTC QLQ- BIL21)
- CT scan to include thorax/abdomen/pelvis to document disease status. *(Patients can be scanned outside of this time-frame if required for clinical reasons).*
- For patients with measurable disease, RECIST (v1.1) measurements must be taken. (SBRT patients who appear to have local disease progression at the 3 month follow up should have a repeat scan to confirm local progression (refer to section 9.7 [Assessments for patients if suspected Disease Progression]) (see Appendix VII [RECIST Criteria version 1.1]).
- MRI scan of liver is strongly recommended
- Blood sample for exploratory research *(at 6 month follow up visit in the absence of PD only)* (see section 10 [Exploratory Biological Studies] for more information)

9.7. Assessments for patients if suspected Disease Progression (at completion of treatment assessment or 3 month follow-up)

- Patients who appear to have local disease progression at the completion of treatment assessment or at the 3 month follow-up assessment should have a repeat response assessment scan 4-6 weeks later to confirm local progression.
- For patients with measurable disease RECIST (v1.1) measurements must be taken.

Table 9: *Confirming disease progression*

Completion of Treatment/ 3 Month follow-up CT Scan	**Status**
CR/PR/SD	Not Disease Progression
PD Uncertain	Repeat scan 4-6 weeks later if still PD then its progression
PD	Disease Progression

9.8. Assessments after Disease Progression

The following should be done at disease progression if the patient progresses prior to 6 month follow up visit:

- Blood sample for exploratory research (see section 10 [Exploratory Biological Studies] for more information)

After documentation of disease progression, patients should be followed up as per standard oncological care for patients. Survival data and data on any further treatment the patient receives will be collected every 3 months for up to two years after registration.

10. EXPLORATORY BIOLOGICAL STUDIES

At the time of trial entry, patients will be consented to donate archival tissue blocks and blood samples for future research. Consent for this collection and for future research will be mandatory for trial patients, except for collection of sample for serum which is optional for trial sites see section 10.4 [Serum Samples (Optional for sites)].

Analysis of the tissue and blood samples will be addressed in separate applications. These applications will be assessed by a Tissue Access Committee. Applicants will be required to provide evidence of adequate funding for their project and the project will need to receive appropriate ethics approval prior to release of any samples.

Refer to the ABC-07 lab manual in the Investigator Site File (ISF) for more details on sample collection, processing, storage and shipment of samples.

10.1. Archival Tissue Blocks

Where possible, a representative archival block of the tumour tissue from a biopsy or prior surgery will be collected for future research. At the end of the trial, the samples will be included in the national Biliary Tract Cancer Virtual Tissue Bank.

10.1.1. Shipping

Tissues blocks should be shipped as soon as possible after entering a patient into the study to address in section 10.5.

10.2. Whole blood samples for Germline DNA

For detailed protocols for the preparation, storage and shipping of blood samples, refer to the ABC-07 Laboratory Manual.

10.2.1. Timing of collection

A whole blood sample for germline DNA will be collected from patients pre-treatment (within 14 days prior to starting CisGem). Blood samples for translational research must not be collected prior to registration.

10.2.2. Preparation of sample

Whole blood should be collected into an EDTA tube. Samples must not be frozen, but may be put into the fridge. Samples must be shipped on the same day as collection.

10.2.3. Shipment

All blood samples should be shipped the same day they are taken in Royal Mail Safe Boxes to the address in section 10.5.

10.3. Whole blood samples for ctDNA

For detailed protocols for the preparation, storage and shipping of blood samples, refer to the ABC-07 Laboratory Manual.

10.3.1. Timing of collection

Whole blood samples for ctDNA will be collected from patients at 4 time points during the trial:

- **Pre-treatment** (within 14 days prior to starting CisGem). This blood sample must not be collected prior to registration.
- **End of cycle 4**
- **Completion of treatment visit** (approximately 1 month post treatment)
- **6 month follow up visit or at disease progression**

Patients who have shown progression at the end of cycle 4 imaging will have samples taken for exploratory research at the pre-treatment and disease progression time-points only.

10.3.2. Preparation of sample

Whole blood should be collected in a 10 mL Streck tube. Samples must not be frozen or refrigerated, as ambient temperature is optimum and must be shipped on the same day as collection.

10.3.3. Shipment

All blood samples should be shipped the same day they are taken in Royal Mail Safe Boxes to the address in section 10.5.

10.4. Serum Samples (Optional for sites)

For detailed protocols for the preparation, storage and shipping of blood samples, refer to the ABC-07 Laboratory Manual. Trial sites may not have the facilities to collect and process the samples for serum, therefore collection for these samples is optional.

10.4.1. Timing of collection

Blood for serum samples will be collected from patients at 4 time points during the trial:

- **Pre-treatment** (within 14 days prior to starting CisGem). This blood sample must not be collected prior to registration.
- **End of cycle 4**
- **Completion of treatment visit** (approximately 1 month post treatment)
- **6 month follow up visit or at disease progression**

Patients who have shown progression at the end of cycle 4 imaging will have samples taken for exploratory research at the pre-treatment and disease progression time-points only.

10.4.2. Preparation of sample

Whole blood should be collected in 1 x 10 mL clot activator tube. Allow to clot, then spin at 2000g for 10 minutes. Pipette the separated serum in to 2 × 2mL cryovials. Samples must be frozen at -80°C (or -20°C if -80°C not available). Store plasma samples at -80°C until the end of the trial or until requested. UCL CTC will arrange for a courier to collect the frozen samples in batches. The courier will arrive with dry ice and packaging material to ensure samples remain frozen during transport.

10.5. Shipping Samples

All biological samples for exploratory research should be shipped to:

Arran Speirs/Victoria Spanswick
UCL ECMC GCLP Facility
Ground floor

UCL Cancer Institute
Paul O' Gorman Building
72 Huntley Street
London
WC1E 6DD

11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed onto trial CRFs and must be verifiable from source data at site. Examples of source documents are hospital records which include patient's notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's initials and trial number must be clearly indicated on all material and any other patient identifiers removed/blacked out prior to sending to maintain confidentiality.

11.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the CRFs must be sent to UCL CTC and a copy kept at site.

11.2. Missing Data

To avoid the need for unnecessary data queries CRFs should be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When required data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

11.3. Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit and within 1 month of the patient being seen.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subject to a 'for cause' monitoring visit. See section 14.2 ['For Cause' On-Site Monitoring] for details.

11.4. Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests (DCRs) will be sent to the data contact at site. Further guidance on how data contacts should respond to DCRs can be found on the DCR forms.

12. PHARMACOVIGILANCE

12.1. Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

12.1.1. Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.4 for AE reporting procedures.

12.1.2. Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

12.1.3. Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" 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)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See section 12.2.5 for SAE reporting procedures.

12.1.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information.

i.e. an adverse event meeting the following criteria:

- Serious – meets one or more of the serious criteria above
- Related – assessed by the local investigator or sponsor as causally related to one or more elements of the trial treatment
- Unexpected – the event **is not consistent** with the applicable reference safety information (RSI)

See section 12.2.5 for reporting procedures for these events.

12.1.5. Overdose, Trial Treatment Error and Occupational exposure

Refer to section 8.7 for details on reporting of these events.

12.2. Reporting Procedures

12.2.1. Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 should be used. This is available online at:

http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

12.2.2. Severity grade

Severity grade of each adverse event must be determined by using the CTCAE v4.03 as a guideline, wherever possible.

12.2.3. Causality

The relationship between a treatment and an adverse event will be assessed. For AEs (including SAEs), the local PI or designee will assess whether the event is causally related to trial treatment. For SAEs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- Related (reasonable possibility) to a trial treatment.
- Not related (no reasonable possibility) to a trial treatment.

NB Events will be classified as related to trial treatment if evaluated as possibly, probably or definitely related by the investigator or sponsor.

UCL CTC will consider events evaluated as related to be adverse reactions.

12.2.4. Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent and 6 months post last trial treatment administration (See section 16.1 [End of Trial] for end of trial definition) must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.5 [Reporting of Serious Adverse Events (SAEs)].

Pre-existing conditions (i.e. conditions present at informed consent) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again).

12.2.5. Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 days post last trial treatment administration **(or after this date if the site investigator feels the event is related to a trial treatment)** must be submitted to UCL CTC by fax or email within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

12.2.6. Severity

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as a guideline, wherever possible. The criteria are available online at:

http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

12.2.7. Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report **unless considered to be related to the trial treatment**, but must be recorded in the relevant sections of the trial CRFs:

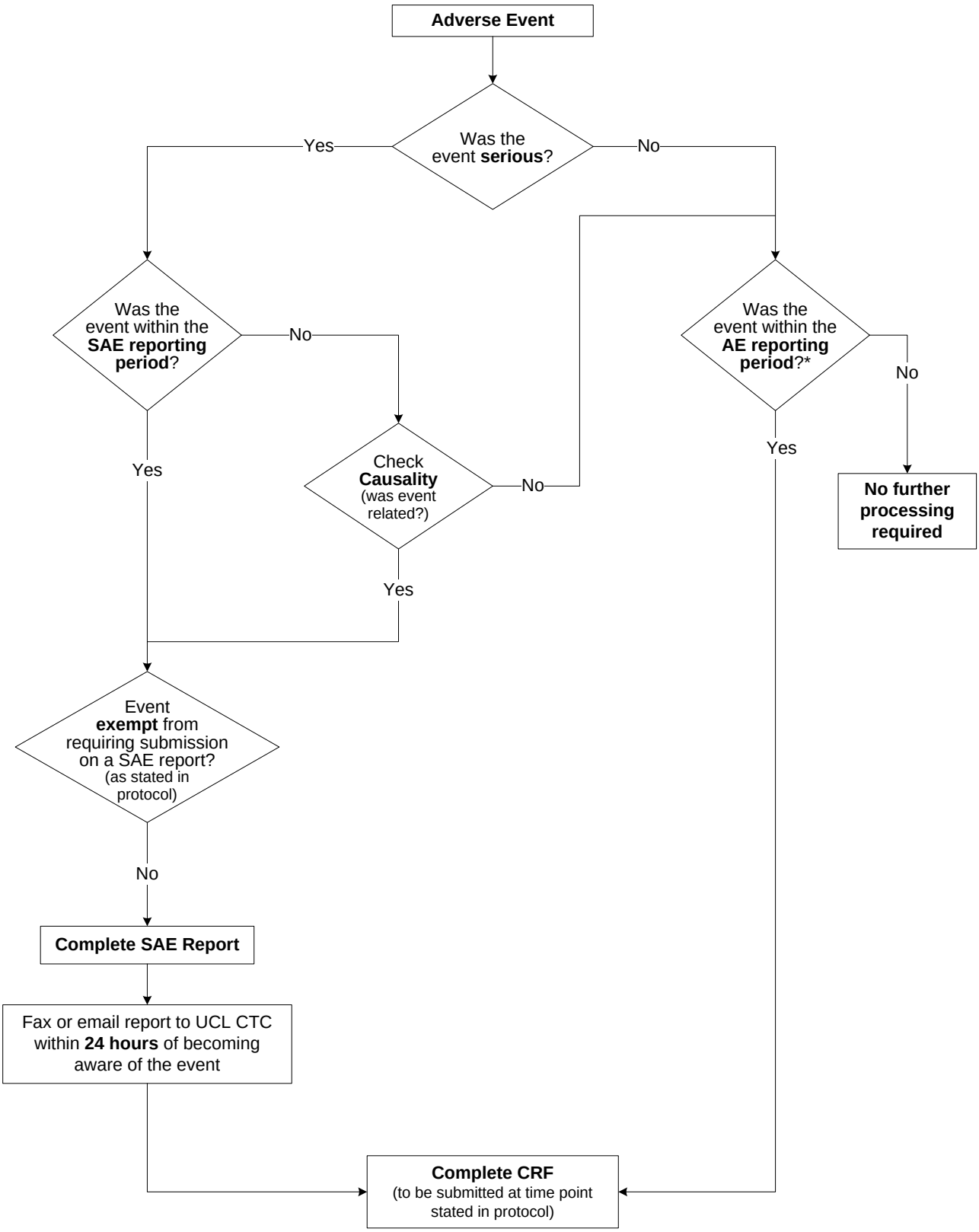
- Events that occur more than 30 days post last trial treatment administration, unless:
    - Considered to be a late effect of the trial treatment
    - It is a pregnancy related event (see section 12.5 Pregnancy Reporting)
- Disease-related events:
    - Disease progression (including disease related deaths)
    - Ascites
    - Biliary tract infection / Biliary Sepsis
    - Cholangitis
    - Ileal perforation/Colonic perforation/Small intestinal perforation
    - Increased alkaline phosphatase if >5 x ULN and <10 x ULN for less than 2 weeks
    - Increased AST
    - Increased ALT if <10 x ULN

NB: that hospitalisation for elective treatment or palliative care or prolongation of hospitalisation for social/logistic reasons does not qualify as an SAE.

Completed SAE Reports must be faxed or emailed to UCL CTC within 24 hours of becoming aware of the event

Fax: +44 (0)20 7679 9871
Email: ctc.abc07@ucl.ac.uk

Adverse Event Reporting Flowchart



*This applies if AE and SAE reporting periods differs.

12.2.8. SAE Follow-Up Reports

UCL CTC will follow up all SAEs until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted. Sites must ensure any new and relevant information is provided promptly. If the event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the updated information is not being reported to UCL CTC within 24 hours of the site becoming aware, the circumstances that led to this must be detailed in the SAE/SAR Report to avoid unnecessary queries.

12.2.9. SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in protocol Appendix V for radiotherapy, and the approved SPCs for cisplatin and gemcitabine.

The CI, or their delegate (e.g. a clinical member of the TMG) will review the SAE and perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI (or their delegate) will be consulted for their opinion at the time.

12.3. SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA within the required timelines. Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

12.3.1. Informing Sites of SUSARs

UCL CTC will inform all sites of any SUSARs that occur on the trial. Sites will receive a quarterly line listing which must be processed according to local requirements.

12.4. Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAE reporting as per section 12.2.7) according to treatment allocation;
- Line listing of adverse reactions to the trial treatment regimen or individual trial treatments;

The IDMC and TMG will review trial safety data to identify:

- A higher incidence of rare serious adverse reactions than is stated in the RSI for a trial treatment;
- Trial related events or incidents that may lead to changes to the trial documents.

In addition, if UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

12.5. Pregnancy Reporting

Reporting period:

For any pregnancy exposure to trial treatment, the site must submit a trial specific Pregnancy Report to UCL CTC by fax or email **within 24 hours** of learning of its occurrence.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient
- Pregnancy in a partner of a male trial patient
- Exposure to treatment in a partner of a male trial patient who was pregnant at the start of the trial

occurring between consent and six months after last administration of cisplatin or gemcitabine, or 12 months post last radiotherapy administration.

The site must request consent from the pregnant trial patient or female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial-specific Pregnancy Monitoring Information Sheets and Informed Consent Forms for trial patients.
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of study patients.

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported to UCL CTC by faxing or emailing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy

Fax: +44 (0)20 7679 9871
Email: ctc.abc07@ucl.ac.uk

12.5.1. Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up at least monthly for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC by fax or email within **24 hours** of learning of the new information. In case of adverse outcome to the pregnancy, reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

12.5.2. SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.5 for details.

12.5.3. Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 [SUSARs] for details.

12.6. Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

13. INCIDENT REPORTING AND SERIOUS BREACHES

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and provided but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2. Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1. Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 4.2.2 [Required documentation] and 6.1 [Pre-screening and Screening Log].

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the registration and randomisation forms will be undertaken by an appropriately trained UCL CTC staff member prior to registration and randomisation. Also refer to section 7.1 [Registration].

Details relating to the informed consent process will be collected on the registration form and are subject to review by CTC as part of patient eligibility.

Copies of completed drug accountability logs will be collected at UCL CTC for all trial patients. Sites will be required to submit logs in accordance with the trial monitoring plan.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.4 [Data Queries].

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk e.g. evidence of an overdose having been administered, indication that dose modification rules for an IMP were not observed following an adverse reaction, etc., the matter will be raised urgently with site staff and escalated as appropriate (refer to sections 13 [Incident Reporting and Serious Breaches

and 14.2 ['For Cause' On-Site Monitoring] for further details).

14.2. 'Triggered' On-Site Monitoring

On-site monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit and confirming when it will take place. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach**.** Refer to section 13 [Incident Reporting and Serious Breaches] for details.

14.3. Oversight Committees

14.3.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and ABC-07 trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly during the recruitment phase (approximately 3 to 4 times a year) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Upper GI Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA.

A TMG charter, which outlines the responsibilities for the ABC-07 trial, must be signed by all members of the committee before the first meeting is held.

14.3.2. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

The ABC-07 trial is reviewed by an established UCL CTC TSC that has oversight of a number of trials. All members have signed a TSC charter.

14.3.3. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held periodically to review interim analyses or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

An IDMC charter, which outlines the responsibilities for the ABC-07 trial, must be signed by all members of the committee before the first meeting is held.

14.3.4. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 [Pharmacovigilance].

15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1. Patients who do not start Trial Treatment

If a patient does not start treatment, the reasons for this must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

If a patient does not start treatment, then the patient should be withdrawn from the trial. Data collected will be used in the trial analysis, where appropriate.. Biological samples collected may still be used unless the patient explicitly withdraws consent to this.

15.2. Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever such treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's notes. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable AR
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment
- Delay of more than 3 weeks of chemotherapy due to AR
- Interruption of radiotherapy of more than 7 days in total due to AR (refer to section 8.6.3 [Interruptions to SBRT] for more information)
- The start of radiotherapy is delayed for more than 7 weeks after the start of cycle 6
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant or male/female fails to use adequate birth control (for patients of childbearing potential)

In these cases patients will remain within the trial for the purposes of follow-up and data analysis unless they explicitly withdraw consent.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

15.3. Withdrawal from the Trial

If a patient expresses their wish to withdraw from the trial, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

15.4. Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of essential safety data, and recorded on the relevant CRF. In this event data due up to date of withdrawal should be submitted but no further data other than essential safety data should be sent to UCL CTC.

15.5. Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer the patient to a participating site, the registering site remains responsible for submission of forms.

Before declaring a patient lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be two years after enrolment of the final patient or once all patients have died, whichever happens first, at which point the 'declaration of end of trial' form will be submitted to the MHRA and Ethical Committee (EC), as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site. Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 25 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 25 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see sections 14.3.2 [Trial Steering Committee (TSC)] and 14.3.3 [Independent Data Monitoring Committee (IDMC)]). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the CTSA.

17. QUALITY ASSURANCE

17.1. Quality Assurance for SBRT

The radiotherapy quality assurance (RT QA) programme for the trial will be co-ordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) group. QA will include pre-trial and on-trial assessments.

Pre-trial QA will involve a pre-trial test case to be delineated by all participating investigators who will be involved in the delivery of SBRT, and another case with contours provided, to be planned by participating RT departments. Feedback will be provided on the delineated volumes and plan prior to site activation.

This study requires a rapid review of contours and plans prior to delivery of SBRT at each SBRT site for at least the first 3 patients registered to be treated there, including at least one patient with a tumour ≤ 6cm and at least one patient with a tumour >6cm. This is expected to take 2 days per plan. The QA process will be reviewed once each site has treated 3 patients and retrospective QA will be considered. If necessary more patients will be reviewed.

Details on the QA programme and all required documentation can be found via the ABC-07 link at www.rttrialsqa.org.uk. A separate document (Radiotherapy QA programme) will be provided to sites and should be adhered to for all ABC-07 trial patients.

17.2. Central review of imaging

Central review of CT images (and additional imaging if required) will be performed for 100% patients from each centre, to exclude patients who have not been randomised. Images from registration up until 6 month follow up will be reviewed.

The following sets of images (CT, and MRI if available) should be pseudonymised and sent together for central assessment to confirm disease status:

- baseline (pre-registration),
- end of cycle 4,
- completion of treatment,
- 3 & 6 month follow-up and
- confirmation of disease progression scan (if applicable).

The patient's initials and trial number must be clearly indicated on all scan images/reports, and any other patient identifiers removed/blacked out prior to sending to maintain confidentiality.

The recommended method of transfer of images is via the Image Exchange Portal / NHS Picture Archiving and Communication System . Images should be pseudonymised prior to electronic transfer and all images should be transferred together once a patient has progressed.

Centres without access to the NHS Secure File Transfer Service / Image Exchange Portal can transfer pseudonymised scans in DICOM format and send by CD after the patient has progressed to:

Dr Prakash Manoharan

The Christie Department of Radiology,

The Christie NHS Foundation Trust,

Wilmslow Road,

Manchester

M20 4BX

18. STATISTICS

18.1. Sample Size Calculation

18.1.1. Feasibility

The feasibility part of the study is testing if an acceptable time frame for recruitment is possible in this rare cancer group, and given the logistical complexities of the trial. The ABC-03 study recruited 16 patients that would have been potentially eligible for ABC-07 in 18 months. Therefore, an average recruitment rate 1 patient/month into ABC-07 should be feasible, and would enable the trial to complete within an acceptable time frame.

We aim to maintain an average recruitment of at least 1 patient/month for 6 months once the first 6 sites have been activated (i.e. from approximately 6 months after the first site activation). Up to 18 patients will be recruited during the feasibility stage of the trial.

18.1.2. Phase II

The trial as a whole is targeting an improvement in the PFS from 45% to 62% at 9 months from randomisation. This reflects an increase of the same magnitude at 12 months after registration (i.e. just before start of CisGem) and will therefore facilitate comparison of our endpoint with other trials. This is equivalent to an extension, from randomisation, of the median PFS from 7.8 to 13.0 months or a target HR 0.60. Assuming a recruitment time of 72 months with a follow-up of 21 months after randomisation, one-sided alpha of 0.15, power 80% and a 2:1 randomisation, the sample size required is 65 patients (43 patients in the experimental arm and 22 patients in the control arm). The sample size was calculated using Power and Sample size Calculations version 2.1.31[38].

In the ABC-03 study >50% of patients with locally advanced disease completed 8 cycles of CisGem. In terms of treatment compliance on average for each cycle ~60% patients completed as per protocol with ~40% having modifications such as dose reduction, delay or both.

A 20% dropout rate has been incorporated into the sample size calculation to account for patients who are registered but not subsequently randomised for whatever reason. Assuming 20% drop out between registration and randomisation, a total of 81 patients are required.

18.2. Populations for Analysis

The feasibility population will include all patients registered in the study.

The primary endpoint of the trial will be performed on an intention-to-treat basis, i.e. all patients randomised will be included, and all patients will remain in their randomised treatment groups whatever treatment they received.

A secondary analysis will also be carried out on a per protocol population. The per-protocol population will consist of all patients who received 80% or greater of their allocated treatment.

All patients who have been exposed to at least one dose of CisGem will be included in the safety analysis.

18.3. Analysis of the Primary Endpoint

18.3.1. Feasibility

Endpoint definition

The primary endpoint is the monthly rate of recruitment into the trial once all required sites have been activated (approximately 6 months after activation of the first site).

The decision to move from feasibility into the full randomised phase II will be based upon achieving the target recruitment rate of 1 patient/month. In February 2017 the TMG agreed to expand the patient population to include patients with tumours up to 12 cm. The change in this inclusion criteria has no effect on the sample size assumptions and therefore there is no change to the sample size required. If the target recruitment remains unachievable after approximately 18 months recruitment in total, then we would conclude that the trial is not feasible.

During feasibility, the number of patients who are alive and progression free at 9 months after randomisation will also be reviewed by the IDMC. This will allow us to assess whether the PFS rate is of the order to warrant continuing recruitment beyond the feasibility phase.

18.3.2. Phase II

Endpoint definition

Progression-free survival (PFS) is the primary endpoint and is defined as the time from patient randomisation to the time a patient experiences a PFS event. PFS events are objective disease progression on CT and/or MRI scans assessed using RECIST v1.1, and death from any cause.

The effect of treatment on progression-free survival will be summarised using Kaplan-Meier curves. Cox regression will be used to assess the effect of treatment on progression-free survival, and hazard ratios, 95% and 70% confidence interval and p-values will be reported.

18.4. Analysis of Secondary Endpoints

18.4.1. Efficacy (secondary)

Endpoint definitions

Progression free survival at 9 months after randomisation: The presence or absence of a PFS event at 9 months after randomisation. The median PFS and 12 months PFS rate will be reported separately by treatment arm. The 12 months PFS rate and median PFS will be obtained for both the CisGem arm and CisGem+SBRT arm, and the 95% confidence intervals calculated.

Best overall response: Best overall response will be assessed according to RECIST v1.1. Confirmation of a complete or partial response is not required. Stable disease will be considered the best response only if a second assessment has been carried out which confirms SD at least four weeks after registration. The proportion of patients whose best overall response is complete or partial will be presented.

Duration of response: The duration of overall response is measured from the time of best overall response until the date of objective disease progression on CT and/or MRI.

Patterns of treatment failure: Sites of treatment failure will be evaluated in terms of local progression, regional progression and distant metastases as outlined below.

Local progression: At least 20% increase in sum of the longest diameters of irradiated target lesion (the target lesion is the measurable disease included in the radiation volume). In addition to a minimum total relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Because radiation changes (specifically in the surrounding liver around the cholangiocarcinoma) may be confused for local progression at the 3 month follow up CT scan, local progression of the irradiated target lesion must also be seen on the follow up CT scan 4-6 weeks later before progression is confirmed. Thus, review of images by experienced radiologists is required, as is the importance of relaying radiation information to the radiologists, to avoid inaccurate labelling of progression when liver changes are due to the radiation effect on the liver.

Regional progression: The appearance of one or more new lesions in the liver or locoregional lymph nodes (such as in the porta hepatis area, cystic duct, common bile duct, hepatic artery and portal vein).

Distant metastases: Unequivocal, unambiguous progression of any measurable and non-measurable disease is defined also as PD. Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathologic lymph node ≥ 10mm and ≤ 15 mm) and any vascular thrombosis. Other non-measureable disease includes ascites and pleural effusions.

Overall survival: Overall survival will be measured from the date of randomisation to the date of death from any cause. The effect of treatment on overall survival will be summarised using Kaplan-Meier curves. Cox regression will be used to assess the effect of treatment on overall survival, and hazard ratios, 95% confidence interval and p-values will be reported.

Downstaging permitting surgery: The proportion of patients achieving downstaging permitting surgery will be presented.

Time to treatment failure: Time to treatment failure is defined as time from the patient starting protocol treatment to the time the patient stops treatment early for whatever reason (disease progression, death, or patient starts next treatment having had trial treatment as scheduled, whichever occurs first). Time to treatment failure will be summarised using Kaplan-Meier curves. Cox regression will be used to assess treatment differences in terms of time to treatment failure. Hazard ratios, 95% confidence interval and p-values will be reported.

18.4.2. Safety

Endpoint definitions

Adverse event: AEs will be graded according to CTCAE v4.03. The worst grade of an adverse event (AE) experienced during treatment will be used. The proportions of patients experiencing a maximum grade of 3 or above adverse event between the treatment groups will be presented.

18.4.3. Health related Quality of Life

Quality of Life (QoL) will be measured using the EQ5D as well as EORTC QLQ- BIL21 questionnaire. The treatment groups will be compared for each of the QoL scales derived from EQ5D and EORTC QLQ- BIL21. Analysis of covariance will be used to assess treatment differences in the quality of life scores at completion of treatment and at 3 months follow-up, adjusting for baseline scores (registration and end of cycle 4).

Also, mixed modelling will be performed to assess treatment differences in the QoL patient trajectories across time. The mean differences in the quality of life scores between treatment groups, 99% CI and p-values will be reported.

18.5. Interim Analyses

Interim data will be reviewed by an independent Data Monitoring Committee (IDMC) at least once a year (see section 14.3.3 [Independent Data Monitoring Committee (IDMC)]). The IDMC will monitor safety, adverse events and efficacy, and can recommend changes to the protocol as well as continuation or closure of the trial. No other interim analyses are planned.

18.5.1. Futility Analysis

As the planned recruitment period is relatively long, futility analyses will be planned into this study. We will evaluate futility of the trial using conditional power. The calculation of the conditional power is informative because it indicates, at each interim analysis, the probability of obtaining a statistically significant result at the end of the study, given the results seen at the interim analysis and assuming that the future data to be collected is consistent with the target hazard ratio (HR). The conditional power calculation incorporates the observed and target number of PFS events and the observed and target PFS HR.

The conditional power for the primary endpoint will be presented to the IDMC committee annually in a closed report, so there will be a futility analysis performed approximately every year. As recommended by Jitlal et al (2012), if the conditional power for the primary endpoint is ≤15% in two successive interim analyses, then the IDMC committee may recommend the trial to be terminated for futility.

19. ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- The principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928.
- Human Rights Act 1998.
- Data Protection Act 2018 and General Data Protection Regulation (EU)2016/679 (GDPR).
- Freedom of Information Act 2000.
- Human Tissue Act 2004.
- Medicines Act 1968.
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice.
- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority.

Where applicable, UCL CTC and sites will work towards implementation of the EU Clinical trials Regulation EU/536/2014.

19.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London- Hampstead Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

19.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

19.3. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Healthboard R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

19.4. Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

19.5. Patient Confidentiality & Data Protection

Patient identifiable data, including patient initials and date of birth will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR with the Data Protection Officer at UCL.

Patient scan images sent for central review will be pseudonymised (labelled with the patient's initials and trial number only), and any other patient identifiers will be removed/blacked out at site prior to sending for central review to maintain patient confidentiality.

Patient identifiable data, including initials only, will be provided to the UCL GCLP facility in order to process the samples (or other reason if different). UCL GCLP Facility will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

20. SPONSORSHIP AND INDEMNITY

20.1. Sponsor Details

Sponsor Name	University College London
Address	Joint Research Office Gower Street London WC1E 6BT
Contact	Director of Research Support
Tel	020 3447 9995/2178 (unit admin)
Fax	020 3447 9937

20.2. Indemnity

University College London 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. University College London does not accept liability for any breach in the hospitals' duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is in 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 University College London 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 University College London, upon request.

21. FUNDING

Cancer Research UK is supporting the central coordination of the trial through UCL CTC and research costs at participating sites.

22. PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG.

The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advise on the nature of publications. If there are named authors, these should include the Chief Investigator, Trial Coordinator(s), and Statistician(s) involved in the trial. Contributing Site Investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible.

Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the TMG. The clinicaltrials.gov number allocated to this trial will be quoted in any publications resulting from this trial.

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APPENDIX 1: ABBREVIATIONS

3D-CRT	Three-dimensional conformal radiation therapy
ABC	Active breathing control
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate aminotransferase
BTC	Biliary Tract Cancer
CBCT	Cone beam computed tomography
CECT	Contrast-enhanced computed tomography
CI	Chief Investigator
CR	Complete Response
CRF	Case Report Form
CSG	Clinical Studies Group
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
DCR	Data Clarification Request
DTPA	Diethylene Triamine Pentaacetic Acid
DSUR	Development Safety Update Report
EBRT	External beam radiation therapy
EDTA	Ethylene Diamine Tetra Acetate
ERCP	Endoscopic Retrograde Cholangiopancreatography
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
GDPR	General Data Protection Regulation (EU)2016/679
GFR	Glomerular Filtration Rate
GTV	Gross tumour volume
HCCA	Hilar Cholangiocarcinoma
Hb	Haemoglobin
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IGRT	Image guided radiotherapy
IMP	Investigational Medicinal Product
IMRT	Intensity modulated radiation therapy
INR	International Normalised Ratio
IRMER	Ionising Radiation (Medical Exposure) Regulations
IV	Intravenous
LC	Local control
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
ITV	Internal tumour volume
MRC	Medical Research Council
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Image
MHRA	Medicines and Healthcare products Regulatory Agency

NCRI	National Cancer Research Institute
NRES	National Research Ethics Service
NSAIDS	Nonsteroidal anti-inflammatory drugs
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PIC	Patient Identification Centre
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance Status
PTC	Percutaneous Transhepatic Cholangiography
PTV	Planning target volume
QoL	Quality of Life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response Rate
RT	Radiotherapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Body Radiotherapy
SD	Stable Disease
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TPS	Treatment planning system
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO PS	World Health Organisation Performance Status
WOCBP	Women of childbearing potential
XP	Capecitabine cisplatin chemotherapy

Appendix I. **CHILD-PUGH SCORE**

Each measure is scored 1-3, with 3 indicating most severe derangement. It is then classified into Child-Pugh class A to C, employing the added score from below.

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	**Class**
5-6	A
7-9	B
10-15	C

Appendix II. **WHO PERFORMANCE STATUS**

Grade	Description
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Appendix III. **RADIOTHERAPY**

All patients randomised to receive SBRT will be planned to receive 5 or 15 fractions of radiotherapy (depending on the size of their tumour as measured on the end of cycle 4 imaging scan). SBRT should start not more than 6 weeks after day 1 of cycle 6, and not less than 2 weeks after the last dose of chemotherapy. The planning CT can be undertaken at the end of cycle 5 or in the 1st week of cycle 6. For lesions ≤6 cm SBRT is to be delivered in 5 fractions over 5 to 15 days at a total dose of 40-50Gy. For lesions >6 cm SBRT is to be delivered in 15 consecutive daily fractions, delivered weekdays over 19 to 21 days at a total dose of 45-67.5Gy.

1. Planning (image acquisition and outlining)

1.1. Patient preparation

Ensure patient has been nil by mouth for 2 hours. Clear fluids <200cc permitted. Consider oral contrast (or water) 100-150cc up to 30 minutes prior to CT if visualisation of duodenum required.

If fiducial markers are used for tracking please ensure that 7 days have elapsed from marker insertion, prior to the planning CT.

1.2. Patient immobilisation

Custom immobilisation is strongly recommended (e.g. vacuum immobilisation, stereotactic body frame, patient positioning boards such as chest board, knee cushions, and/or breath hold immobilisation with abdominal compression or active breathing control). All patients will be treated supine, with arms displaced out of the field, unless treated with CyberKnife or other tracking technology that extends treatment time to >30 minutes.

1.3. Planning CT image acquisition

A liver protocol CT must be obtained for treatment planning. This should be a multiphase CT, performed with IV contrast, in exhale breath hold delayed phase 40-45 sec after contrast administration (a non-enhanced phase, an arterial phase and a delayed phase, can be acquired depending on the local site protocol). If the tumour is at the dome of the liver consider scanning the whole lungs to aid lung DVH definition. The contrast enhanced exhale breath hold CT will be the primary image dataset used for outlining.

A 4D CT should follow the contrast enhanced CT. This is mandatory unless tracking is used for treatment delivery (e.g. CyberKnife). Sites using tracking may also choose to perform a 4D CT to check that the implanted fiducials are good surrogates of tumour motion.

The 4D CT scan should be used to confirm the exhale breath hold position of the liver protocol CT.

If the patient was unable to breath hold, the average phase CT obtained from the 4D CT may be used as an alternative to the exhale breath hold CT as the primary dataset for planning.

If there are contraindications to IV CT contrast, contrast multiphase MR can be used to define the gross tumour volume (GTV). This should be fused to the primary planning dataset to aid target definition. Exhale breath-hold is desired as it is most often close to the average position than inhale breath-hold. Exhale is more reproducible than inhale. CT scans obtained during free breathing are strongly discouraged due to poor image quality secondary to motion artefact.

Diagnostic image sets may be fused to the primary dataset to aid target delineation, using rigid registration. If image registration is undertaken the liver, rather than bony anatomy should be registered to each other for target delineation. The area where registration should be focused is the area where the tumour is located if there is rotation or deformation between images.

1.4. Scan limits and slice thickness

The recommended scanning levels for all CT scans are from the carina to below the kidney. A maximum slice thickness of 3mm is permitted.

1.5. Breathing motion management

Measures to quantify and mitigate motion are strongly recommended. Measurement of target/liver breathing motion is required, unless breath hold or fiducial marker tracking is to be used for liver immobilisation/monitoring during treatment.

The minimum requirement for fiducial insertion: 3-4 fiducials a minimum of 2 cm apart, non-collinear position with geometrical centre of fiducials as close as possible to the tumour centre of mass.

Motion may be assessed using 4D CT, fluoroscopy and/or cine MRI. Breathing motion management is recommended if breathing motion is > 5 mm.

The following are options for motion mitigation, active breathing control (ABC) or abdominal compression. Respiratory gating with an external marker is not permitted.

Breathing motion assessed on 4D CT and adequately treated with the planning target volume (PTV) margins < 20mm is permitted without treatment time motion management (gating, tracking, ABC, etc.).

2. Localisation of the target volume and organs at risk

2.1. Nomenclature

Consistent naming of contoured structures used in radiotherapy treatment planning is essential to facilitate the comparison of dose-volume statistics across patients for quality assurance and outcomes analysis. Maintaining consistency in structure names is particularly important (and challenging) in multi-institutional clinical trials, in which treatment planning data are collected from many participating institutions.

A scheme for uniform naming of the structures for ABC-07 is provided in Table 1. The nomenclature must be applied for treatment planning in all trial patients.

2.2. Target definition

Tumour volume and normal tissue definition should be discussed with radiology and joint contouring is recommended.

The Gross Tumour Volume (GTV) is defined as all parenchymal enhancing disease. If nodal disease is treated this should be called GTV_N. Parenchymal disease and nodal disease can be combined if in proximity (less than 1cm between targets and no gastro-intestinal tract luminal structures included in the combined volume).

Clinical target volume (CTV) = GTV

The PTV aims to compensate for set-up and internal organ motion.

The PTV is a volumetric concept and is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible volumetrical variations and inaccuracies in order to ensure that the prescribed dose is delivered to the CTV. A margin will be added to the CTV, in all directions, to produce the PTV, in line with ICRU 50, 62 and 83 recommendations, and should not be edited.

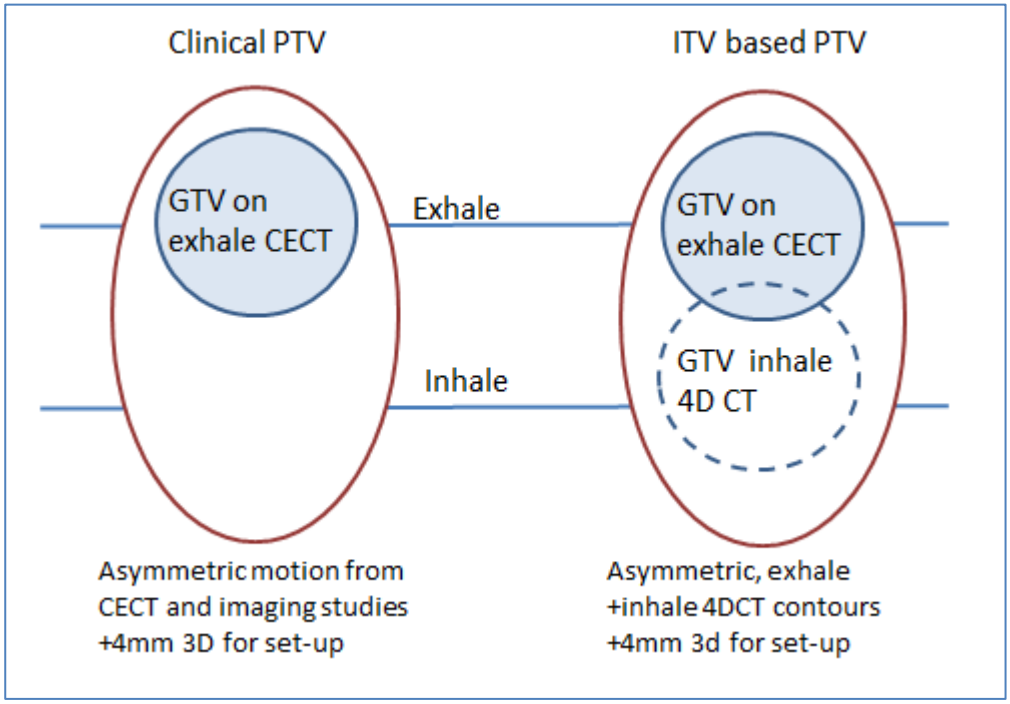
A minimum PTV margin of 4 mm around CTV is required in all directions (for example if fiducial markers and tracking are used).

The range of motion can be assessed on 4D CT using liver as a surrogate for tumour, on cine MRI using tumour directly, and on fluoroscopy using the diaphragm as a surrogate for tumour position. Once motion range is established for the cranio-caudal direction apply asymmetric margins 1-2 mm superiorly and the remaining range of observed motion inferiorly, then circumferentially apply motion symmetrically.

To this volume then apply 4 mm in 3D for set-up uncertainties. The maximum permitted PTV margin is 20 mm and justification for not using motion management should be given. PTV margins ≤ 10 mm are preferable.

Figure 1 below shows the schema of planning target volume (PTV) strategies. Clinically, the gross tumour volume (GTV) was delineated on exhale breath hold contrast enhanced CT (CECT)).

Figure 1.



Alternatively, outline GTV on 3D exhale breath hold and 4DCT phases then combine to form an ITV, then add a uniform margin e.g. 5mm, to give PTV.

2.3. Organs at risk (OAR) definition

The following organs at risk should be outlined and defined as below:
Spinal Canal: Outline the spinal canal from 2cm above to 2cm below the PTV. If non-coplanar beams are used, a greater length should be outlined.

Spinal Canal Planning Risk Volume (PRV): Spinal canal + 0.5cm isotropic margin.

Liver: The whole liver should be outlined.

Liver minus GTV: Liver contour minus the GTV contour (use treatment planning system (TPS) operators to perform the function).

Kidneys: Both kidneys should be outlined separately.

Stomach: The whole stomach should be outlined.

Duodenum: The whole of the duodenum from below the pylorus to the fourth part of duodenum (up to the ligament of Treitz) should be outlined.

Small Bowel: Individual loops of small bowel should be outlined on all slices from 2 cm above to 2 cm below the PTV not including colon and duodenum. If non-coplanar beams are used, consider outlining further loops.

Colon: Large Bowel- The transverse colon should be outlined.

CBD: Common bile duct and bifurcations- These ducts should be identified as tubular structures (lumen density equivalent to water). The expected location of the bile ducts is, the CHD (common hepatic duct) is anterior to the portal vein, lateral to the hepatic artery, and surrounded by fat in the porta hepatis, and the CBD was within or adjacent to the parenchyma of the pancreatic head. If there is uncertainty on the location, the portal vein can be contoured from the splenic confluence to the first bifurcation of the left and right portal veins, then expanded by 15 mm to define the central bile ducts structure.

Heart: The heart will be contoured along with the pericardial sac using mediastinal windowing. The superior aspect (if included in images acquired) for the purpose of contouring is defined as the superior aspect of the pulmonary artery (as seen on coronal reconstruction of the CT) and the caudal border should be defined by the lowest part of the left ventricle's inferior wall that is distinguishable from the liver.

Skin: defined as 0.5 cm inner rind of body contour contoured if adjacent to PTV and in regions receiving more than 10Gy.

Chest wall: defined as 3 cm inner rind of the body contoured if adjacent to PTV and in regions receiving more than 10Gy.

Oesophagus: contour the normal circumference of oesophagus from the gastro-oesophageal junction to carina.

3. Radiotherapy planning

A minimum of 5 beams is recommended. There is no class solution for treating liver tumours and depending on technique coplanar and/or non-coplanar beams or arcs can be used. Beam/arc angles and or location may be individualised to minimise the path length through the liver and through adjacent organs at risk. Aims of planning are to maximise dose to the PTV while maintaining all normal tissue constraints. Reducing the maximal dose to all luminal gastrointestinal normal tissues should be a planning priority to reduce the risk of gastrointestinal toxicity.

The intent is for at least 95% of the prescription dose to cover 95% of the PTV (D95≥95%). This should ensure that the GTV receives 100% of the prescribed dose.

A linear accelerator with at least 6 MV should be used, capable of daily image guidance and IMRT delivery. IMRT with stationary gantry or rotating gantry technique are permitted. Prior IMRT accreditation is necessary through the National RTTQA group. All dose distributions must include corrections for tissue heterogeneities.

3.1. Selection of prescription dose

Total prescription dose based on normal tissue constraints may be either:

50Gy, 45Gy or 40Gy in 5 fractions for patients with tumour size ≤6cm

Or

45Gy, 58.1Gy or 67.5Gy in 15 fractions for patients with tumour size >6cm and ≤12cm

(also see below flowchart)

The final PTV dose is based on the volume of normal liver irradiated, as well as proximity to duodenum, stomach and small bowel. If normal tissue constraints cannot be met, lowering the PTV dose in the overlap area with GI tract should be considered initially, followed by dose reduction in the total prescribed dose.

If tumour is located away from luminal GI structures, the PTV dose prescription should be as high as possible based on mean liver dose (see flowcharts below and tables for each fractionation).

If tumour is located outside of the liver (e.g. nodal recurrence) and there is close proximity to luminal structures, a reduction on the prescribed dose (refer to flowchart) should be considered initially and a mandatory PTV ≥ 80% could be accepted to minimise risk of severe toxicity. For these patients tumour motion management is mandated.

Flowchart for PTV prescription dose based on liver tolerance:

5 fractions SBRT for tumours ≤6cm

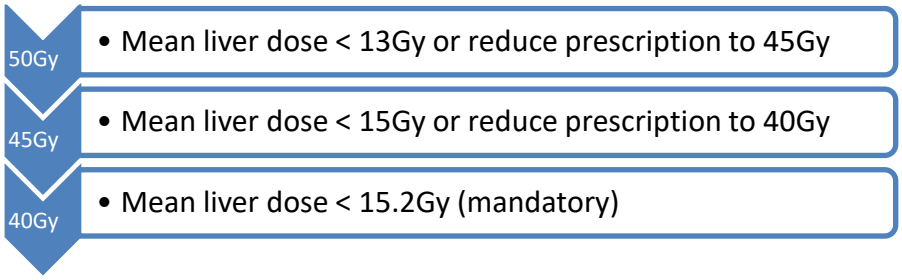


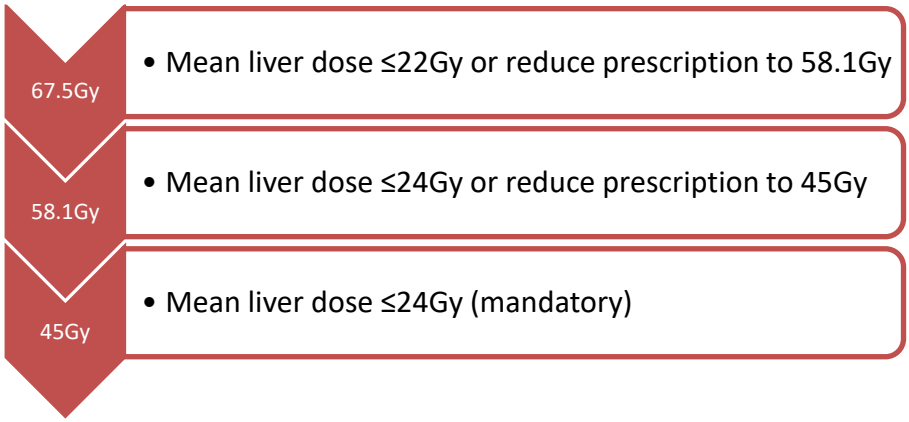
Table 1. Naming convention and constraints for SBRT 5 fractions

Description	Naming Convention	Constraint	Optimal	Mandatory
PTV	PTV_XXXX‡	D95%	≥ 95%	≥ 90%
		DMax (0.1cc)	<120%	<130%
Duodenum	Duodenum	DMax (0.5cc)	-	≤ 35Gy
		D1cc	< 33Gy	-
		D5cc	< 25Gy	-
		D9cc	< 15Gy	-
		D10cc	-	< 25Gy
Stomach	Stomach	DMax (0.5cc)	< 33Gy	≤ 35Gy
		D5cc	< 25Gy	-
		D10cc	-	< 25Gy
		D50cc	< 12Gy	-
Small Bowel	Small Bowel	DMax (0.5cc)	≤ 30Gy	≤ 35Gy
		D5cc	< 25Gy	-
		D10cc	-	< 25Gy
Oesophagus	Oesophagus	DMax (0.5cc)	<32Gy	<34Gy
Liver	Liver	na	na	na
Liver minus GTV	Liver_nonGTV	V10Gy	< 70%	-
		Mean liver dose*	< 13Gy*	≤15.2
Combined Kidney Left Kidney Right Kidney	Kidney Kidney_L Kidney_R	Mean kidney dose	< 10Gy	-
If solitary kidney or if one kidney mean dose >10Gy	Kidney_R or Kidney_L	V10Gy#	< 10%	≤ 45%
Spinal Canal PRV	SpinalCanal_05	DMax (0.5cc)	-	≤ 25Gy
Large Bowel	Colon	DMax (0.5cc)	<32Gy	-
Heart	Heart	DMax (0.5cc)	<27Gy	<29Gy
Common Bile Duct†	CBD	DMax (0.5cc)	<50Gy	-
Skin	Skin	DMax (0.5cc)	<32Gy	
Chest wall	Chest Wall	DMax (0.5cc)	<50Gy	

‡ denote prescription dose. E.g. if 40Gy prescribed PTV_4000, if 67.5Gy prescribed PTV_6750.
†CBD constraint not applicable if tumour located in the CBD
* see flowchart above for dose reduction based on liver tolerance
# The reported values should be a) to the kidney receiving the higher dose and b) the combined kidney dose.

No separate nodal volume is permitted in the 5 fractions protocol. If involved nodes are at a distance from tumour GTV treat under 15 fraction protocol.

15 fractions SBRT for tumours >6cm and ≤12cm:



If lymph nodes are at a distance from the primary GTV the prescription for nodal PTV should be 40.5Gy in 15 fractions.

Table 2. Naming convention and constraints for SBRT 15 fractions

Description	Naming Convention	Constraint	Optimal	Mandatory
PTV	PTV_XXXX‡	D95%	≥ 95%	≥ 90%
		DMax (0.1cc)	<120%	<130%
Duodenum	Duodenum	DMax (0.5cc)	≤45	≤48
		D1cc	-	-
		D5cc	≤36	-
Stomach	Stomach	DMax (0.5cc)	≤40	≤45
		D5cc	≤36	
Small Bowel	Small Bowel	DMax (0.5cc)	≤45	≤48
		D5cc	≤36	
Oesophagus	Oesophagus	DMax (0.5cc)	≤45	≤48
Liver	Liver		na	na
Liver minus GTV	Liver_nonGTV	Mean liver dose*		
Combined Kidney Left Kidney Right Kidney	Kidney Kidney_L Kidney_R	Mean combined kidney dose	≤12	≤15
If solitary kidney or if one kidney mean dose >12Gy	Kidney_R or Kidney_L	V12Gy#	-	≤10%
Spinal Canal PRV	SpinalCanal_05	DMax (0.5cc)	≤35	≤37.5
Large Bowel	Colon	DMax (0.5cc)	≤48	≤51
Heart	Heart	D30cc	≤45	-
Common Bile Duct†	CBD	DMax (0.5cc)	≤70	-
Skin	Skin	DMax (0.5cc)	≤48	-
Chest wall	Chest Wall	DMax (0.5cc)	≤70	-

‡ denote prescription dose. E.g. if 45Gy prescribed PTV_4500, if 67.5Gy prescribed PTV_6750
†CBD constraint not applicable if tumour located in the CBD
* see flowchart above for dose reduction based on liver tolerance
# The reported values should be a) to the kidney receiving the higher dose and b) the combined kidney dose.

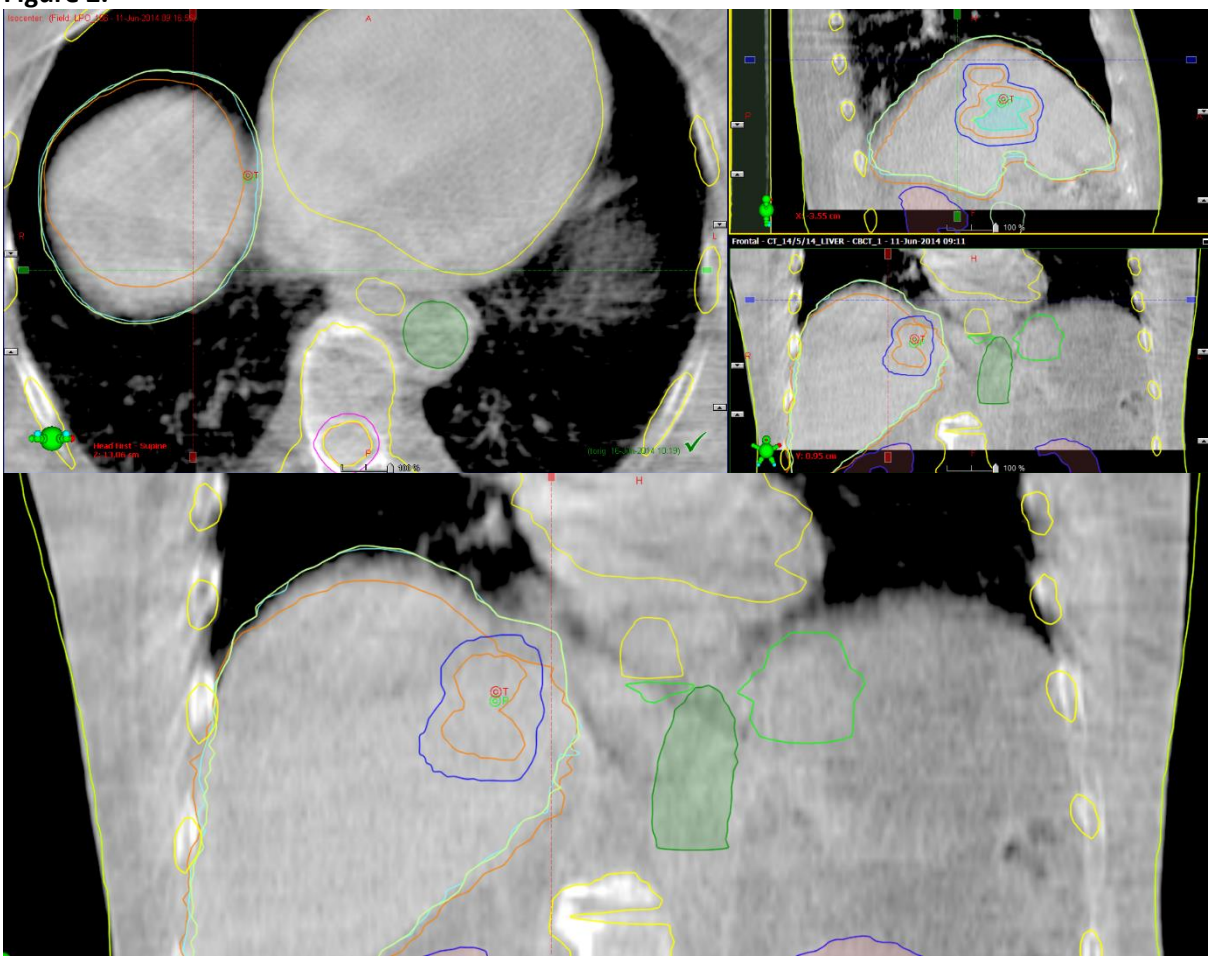
Radiotherapy treatment delivery

If oral contrast is used at simulation, similar timing and volume of oral contrast are suggested to be used prior to each fraction of treatment delivery. On-line imaging prior to each fraction of radiotherapy is mandatory (MV imaging is not permitted) using cone beam CT (CBCT) or kV imaging for CyberKnife. If non-coplanar fields are used, repeat imaging should be undertaken for each non-coplanar field. If on the treatment couch for more than 30 minutes consider repeat CBCT as in keeping with your departmental protocol.

If CBCT is used make sure the dome of diaphragm is in the cone beam field of view. Create inhale and exhale liver contours from the representative phases of 4D CT. Once cone beam is acquired aim for a soft tissue match using liver to liver contour and the blurred area of diaphragm between inhale exhale liver contours.

Figure 2 shows CBCT match in free breathing the inhale and exhale contours are used to guide the liver.

Figure 2.



If fiducial markers are used match to fiducial markers on line correction is required for any shifts >3mm. If 6 degree of freedom correction couch available aim to correct rotations >mm and <3 degrees.

For CyberKnife users please track fiducials and correct for rotations <3degrees. If rotations >3 degrees reposition patient.

4.1 Follow up

A clinical assessment, biochemistry and imaging (CT) will be required at approximately 4 weeks following radiotherapy (see section 9.6 [Assessments during follow up]). Subsequently, patients should be followed up every 3 months until disease progression, or for up to a maximum of 2 years following registration. After documentation of disease progression, patients should be followed up as per standard oncological care. Survival data and data on any further treatment the patient receives will be collected every 3 months for up to two years after registration.

For full details please see section 9.6 [Assessments during follow up] and section 9.8 [Assessments after Disease Progression].

4. Treatment scheduling and gaps

For tumours ≤6cm, the time between fractions should be between 24 and 72 hours, with the preferred interval of 48 hours. Ideally all SBRT treatment should be completed within 15 calendar days. An acceptable variation is within 16 to 21 calendar days. It is unacceptable for treatment to be delivered in more than 21 calendar days.

For tumours >6cm, the patients should be treated on consecutive weekdays. Ideally all treatment should be delivered over 19-21 days. It is unacceptable for treatment to be delivered in more than 34 calendar days.

Appendix IV.**EXPECTED ADVERSE EVENTS FOR RADIOTHERAPY**

The following AEs [39-41] are associated with SBRT and will be considered expected for this treatment:

System Organ Class	Event term	Frequency
Gastrointestinal disorders	• Abdominal pain	Common (20-100%)
	• Dysphagia • Nausea • Gastritis • Gastroparesis • Gastroesophageal reflux disease. • Haemorrhage (oesophageal/colonic/duodenal/upper gastrointestinal/lower gastrointestinal, ileal/jejunal/gastric) • Oesophagitis • Vomiting • Ulcer (oesophageal/colonic/duodenal/small intestine/ ileal/jejunal/gastric) • Fistula (oesophageal/colonic/duodenal/ileal/jejunal/gastric/gastrointestinal) • Perforation (oesophageal/colonic/ duodenal/small intestine/ileal/ jejunal/gastric) • Stenosis (oesophageal/colonic/ duodenal/small intestine/ileal/jejunal/gastric)	Infrequent (5-20%)
General disorders and administration site conditions	• Fatigue	Common (20-100%)
Hepatobiliary Disorders	• Fistula (biliary/gall bladder) • Perforation (bile duct) • Stenosis (bile duct/gall bladder)	Infrequent (5-20%)
Injury, poisoning and procedural complications	• Dermatitis radiation	Common (20-100%)
	• Fracture (Rib)	Infrequent (<10%)
	• Radiation-induced liver disease (RILD)*: Classic RILD is a clinical diagnosis of anicteric ascites (fatigue with weight gain, hepatomegaly*, normal bilirubin, alkaline phosphatase increased (grade 3 or more) (>10 x ULN) and ALT and AST increased (no more than grade 1)) that may occur 2 weeks to 3 months following radiation to the liver. RILD can lead to liver failure that could lead to death.	Rare (<5%)

Investigations	Temporary asymptomatic changes in haematological parameters such as: • Anaemia • Platelet count decreased • Neutrophil count decreased • Lymphocyte count decreased • White blood cell decreased • Proteinuria • Aspartate aminotransferase increased • Alkaline phosphatase increased • Blood bilirubin increased • GGT increased • INR increased	Common (20-100%)
Musculoskeletal and connective tissue disorders	• Chest wall pain	Infrequent (<10%)
Skin and subcutaneous tissue disorders	• Pruritus	Common (20-100%)
Renal and urinary disorders	• Chronic Kidney disease	Rare (<1%)

**MedDRA v19.1, October 2016*

Appendix V. **SCHEDULE OF ASSESSMENTS**

Assessment	Registration		Chemotherapy				SBRT		Completion of treatment	Follow up
	Ideally within 28 days (& no more than 42 days) prior to registration	Within 7 days prior to registration	*Pre-treatment (within 7 days prior to cycle 1 day 1)**	Every chemo cycle (1-8)[1]		End of cycle 4[3]	Pre-SBRT	During SBRT (once a week)	Post treatment	Every 3 months (+/- 4 weeks) for 2 years
				Day 1	Day 8		30 days +/- 7 days prior to commencing SBRT		28-35 days after last dose of CisGem or last fraction of SBRT	
Informed consent	X									
MRI scan of liver [a]	X					X			X[n]	X[n]
CT scan	X					X			X[n]	X[n]
Histological/cytological confirmation of BTC	X [#]									
Medical History		X								
Physical exam [b]		X	X	X			X	X	X	
Vital signs [c]		X	*X*	X			X	X	X	
WHO Performance Score		X	*X*	X	X		X	X	X	X
FBC + differential [d]		X	*X*	X	X		X	X	X	X[i]
Serum biochemistry [e]		X	*X*	X	X		X	X	X	X[i]
INR			X				X	X	X[h]	X[j]
Child-Pugh score							X	X		
Estimation of renal function[f]		X	X	X	X					
CA19-9			X[2]	X			X		X	X[k]
Pregnancy test *(for WOCBP)*		X	X				X[o]			
Audiogram [g] *(if applicable)*		X		X[4]						
QoL questionnaires			X[2]			X			X	X
Whole blood (ctDNA) & serum collection			X[2]			X			X	X[L]
Whole blood (Germline DNA) collection			X[2]							
Shipment of archival tumour tissue			X[m]							
Chemotherapy (CisGem)				X	X					
Concomitant medications		X								
Adverse events		*X*----------*X*								X[i]
Survival		*X*----------*X*								

* required if pre-registration evaluations were performed more than 7 days prior to the start of cycle 1

confirmation not required within 28 days of registration

[1] within 3 days prior to day 1 & day 8 except cycle 1 (see pre-treatment evaluations. Arm A patients cycle 1-6; Arm B patients cycle 1-8;

[2] should be done within 14 days prior to the first dose of any trial treatment. Blood samples for exploratory research must not be collected prior to patient registration.

[3] Visit should be done between 2 and 4 weeks after day 1 of cycle 4. End of cycle 4 CT scan can be performed from Cycle 4 Day 8 onwards.

[4] prior to cycle 2 only for patients with mildly impaired hearing or tinnitus

[a] MRI (strongly recommended)

[b] physical exam, in addition to height (pre-registration only) and weight (pre-chemo and during chemo only)

[C] pulse, blood pressure and temperature

[d] haemoglobin, white blood cell, neutrophil, platelets

[e] sodium, potassium, magnesium, urea, creatinine, phosphate, albumin, corrected calcium, total bilirubin, ALP, AST and/or ALT, LDH

[f] renal function will be estimated using a validated creatinine clearance calculation. For patients who required an isotope clearance test at study entry to confirm adequate renal function refer to **section 8.5.3**

[g] recommended for patients with mildly impaired hearing or tinnitus

[h] SBRT patients only

[i] 3 & 6 month follow up only

[j] SBRT patients only at first 3 month follow up only

[k] 6, 12 & 18 month follow up only

[L] 6 month follow up only/progression Patients who have shown progression at the end of cycle 4 scan will have samples taken at pre-treatment and disease progression time-points only.

[m] Tumour block should be shipped as soon as possible after entering a patient into the trial

[n] not required for patients who progress after 4 cycles

Appendix VI. **DISEASE ASSESSMENT CRITERIA**

1.0 RECIST Criteria Version 1.1

Disease should be evaluated using RECIST Criteria Version 1.1 [42]. Disease progression should be assessed as per the below:

Local progression: At least 20% increase in sum of the longest diameters of irradiated target lesion (the target lesion is the measurable disease included in the radiation volume). In addition to a minimum total relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Because radiation changes (specifically in the surrounding liver around the cholangiocarcinoma) may be confused for local progression at the 3 month follow up CT scan, local progression of the irradiated target lesion must also be seen on the 6 month follow up CT scan before progression is confirmed. Thus, review of images by experienced radiologists is required, as is the importance of relaying radiation information to the radiologists, to avoid inaccurate labelling of progression when liver changes are due to the radiation effect on the liver.

Regional progression: The appearance of one or more new lesions in the liver or locoregional lymph nodes (such as in the porta hepatis area, cystic duct, common bile duct, hepatic artery and portal vein).

Distant metastases: Unequivocal, unambiguous progression of any measurable and non-measurable disease is defined also as PD. Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathologic lymph node ≥ 10mm and ≤ 15 mm) and any vascular thrombosis. Other non-measureable disease includes ascites and pleural effusions.

The ABC-07 trial is using a modified version of RECIST Criteria Version 1.1 [42] as the baseline scans are performed ideally within 28 days up to a maximum of 42 days prior to registration, and patients will commence treatment within 28 days of registration.

2.0 Non-Measurable Disease

Disease progression for patients that did not have measureable disease prior to registration will be defined for the ABC-07 trial as one of the following:

- The appearance of one or more new lesions, or
- An increase in tumour volume representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). To undertake this measurement measure GTV volume on CT and import the relevant image on the system and segment the disease as per protocol then measure volume. Please liaise with Clinical Oncologist that has treated the patient to define the volume, or
- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'.

Wording adapted from http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Appendix VII. PROTOCOL VERSION HISTORY

Protocol:		Amendments:		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	28/05/15			
2.0	03/09/15	1.0	Throughout 1.1 7.2 8.11.1 9.3.3 9.4.1 9.5 9.6 9.7 10.2 10.3 10.4 14.1	Minor clarifications and corrections Dr Prakash Manoharan added to the TMG. Addition of serum samples Addition of two stratification factors Detail added to drug accountability Updated to include QoL and blood sample at end of cycle 4 Change to pre-SBRT assessments time frame Change of section heading to 'Completion of Treatment' and clarification added for some assessments Change of section heading to 'Assessments during follow up' Removal of physical examination and addition of performance status Detail added to assessments after disease progression Change of section heading to 'Whole blood samples for Germline DNA' Detail added about timing and preparation of whole blood sample for germline DNA Addition of section 'Whole blood sample for ctDNA' including details about timing, preparation and shipment Addition of section 'Serum Samples (optional for sites) including details about timing, preparation and shipment Detail added to central monitoring Update to the end of trial definition Detail added to Radiotherapy Schedule updated in line with changes to assessments

			16.1 Appendix IV Appendix VI	
2.1	23/10/15	2.0	8.3.2 10.4.1	Infusion volumes amended to reflect standard practice Name of visit updated to 'completion of treatment visit'
3.0	19/04/17	6.0	Front Cover Throughout 6.2.1 6.2.1 6.2.1 6.2.1 6.2.2 6.4 7	CRUK logo and ISRCTN number added Minor clarifications and corrections Natasha Hava, Jonathan Teague and Hasan Malik added to the TMG Abby Sharp removed from TMG Telephone number for general enquiries updated Change to inclusion criteria: (patients with cancer of the gall bladder are excluded, patients can have involved local nodes if the disease is ≤12cm in longest dimension in total) Inclusion criteria updated to include patients without measurable disease if their tumour is visible on imaging to be targeted with radiation. Inclusion criteria changed to include larger tumours up to 12cm in longest dimension (previously 6cm) Correction to inclusion criteria, albumin level must be >25g/L Early Prostate cancer patients added as an exception to the exclusion criteria Pregnancy test prior to starting SBRT added and definition of WOCBP. Risk for pregnancy and contraceptive advice updated. Telephone number for general enquiries updated Guidance added for patients allocated to SBRT arm to be given SBRT diary to record AEs Information for 15 fractionation regime added. Week numbers added to figure 8A Guidance added to this section to refer to figure 8-A for delays of up to one week. Information for 15 fractionation regime added. Information for 15 fractionation regime added.

			7.2	Guidance for management of overdoses, trial treatment error and occupational exposure added.
				Respiratory rate is not a required assessment at any time-points.
			8.2	EORTC QLQ- BIL21 QoL form added at time-points for EQ5D form
				Pre-registration scans can now be performed within 42 days prior to registration (previously 28 days)
			8.4.2 8.5	Clarification added that patients should meet inclusion criteria for haematological, renal and liver function before starting treatment.
			8.6	Assessments can now be carried out within 3 days prior to cycle 2-8 day 1 (previously within 2 days)
			8.7.3	Quality of life and blood samples for exploratory research added to list of assessments at the end of cycle 4.
			8.8	Weight is not a required assessment prior to starting radiotherapy, while on radiotherapy or on completion of treatment.
				Pregnancy test prior to SBRT has been added
			9	A new section was added for assessments required to confirm disease progression in SBRT patients.
			9.1	Updates and clarifications throughout.
				Event terms changed to CTCAE terms.
			9.2	Pregnancy reporting guidance added.
				Patient withdrawal section updated.
			9.3.1	Statistics for Quality of life updated as a new questionnaire has been added.
				List of abbreviations updated
				Event terms changed to CTCAE terms
			9.3.3	All references of spinal cord changed to spinal canal. Guidance for tumours located outside of liver added. Information for 15 fractionation regime added.
			9.4, 9.5, 9.6	Schedule updated in line with changes to assessments section
				Description of how to assess response in patients without measurable disease. Modifications to RECIST v1.1 described.
			9.4.1	

			9.7 12 12.2.7 12.5 15 18.4.3 Appendix 1 Appendix V Appendix IV Appendix VI Appendix VII	
4	23/1/19	10	Throughout	Minor clarifications and corrections
			TMG	Jonathan Teague removed from TMG. Sandy Beare replaced by Laura White on the TMG. Ganesh Radhakrishna added to TMG
			1.2	Added more detail regarding SBRT to the trial schema
			2.6	BILCAP trial data included
			3.2.2	New endpoint added: Time to treatment failure
			6.2.1	Change to inclusion criteria: ampullary carcinomas will not be eligible.
			6.2.2	Clarifications to the exclusion criteria for patients with previous malignancies.
			6.4.1	Clarification to definition of WOCBP.

4	23/1/19	10	8	SBRT Trial Treatment section moved to after chemo trial treatment section therefore section 8 numbering has been updated to reflect this move.
			8.3.2	BSA should be recalculated in case of weight variation of greater than 10% (previously 5%) from start of treatment.
			8.5	Reminders added that Investigators should use their clinical judgement when managing AEs. Clarification added that gemcitabine should only be reduced by 25%, and up to 50% in case of myelosuppression, according to protocol.
			9	Assessment of GGT (gamma glutamyl transferase) and total protein is no longer required at any time-points.
			9.1	Note added that TNM version 7 should be used throughout the trial.
			9.6	Follow-up assessments should be performed every 3 months +/- 4 weeks (previously +/- 1 week). Note added that scans can be performed outside of this time range if required for clinical reasons.
			9.7	CT scan to confirm suspected disease progression should be performed for all patients (not just patients that receive SBRT) and should be performed 4-6 weeks after the completion of treatment scan or 4-6 weeks after 3 month follow-up (previously 4-6 weeks after 3 month follow-up).
			10	Reminder added that blood samples for translational research must not be collected prior to patient registration. Clarification to blood samples required for exploratory research if patients show disease progression at end of cycle 4 scan.
			12.2	SAEs and pregnancy reports can now be submitted by email (as well as Fax).
			12.2.7	Clarification that exemptions for SAE reporting are for disease related events.
			12.4	Safety monitoring will include assessment of whether disease-related events appear to be enhanced by the trial treatments.
			12.5	Updated guidance for pregnancy reporting and duration of follow-up reporting of pregnancies.

4	23/1/19	10	17.2	Central Review: CT and MRI Quality Assurance will be performed for 100% patients, excluding those not randomised.
			18	Sample size has been reduced from 83 patients to 81 patients.
			18	PFS will now be measured at 9 months from randomisation as patients will have 3 months of treatment between registration and randomisation.
			18.4.3	Analysis of Quality of Life questionnaires clarified.
			19.5	NHS Number will not be collected for patients on the trial.
			Appendix VI	GGT and total protein assessments removed as no longer required. Correction to number of days prior to treatment for treatment cycles 2 onwards. Follow-up assessments should be performed every 3 months +/- 4 weeks (previously +/- 1 week).
			Appendix VII	Removal of reference to RT planning scan for patients with non-measurable disease as RECIST will be performed for all patients whether they have SBRT or chemotherapy only.
5	06/08/2020	15	Throughout	Minor Clarifications and Corrections
			TMG	Marian Duggan replaced by Hayley Cartwright as Senior Trial Coordinator. Natasha Hava replaced by Emma Diggines as Trial Coordinator.
			6.2.1	Inclusion criteria and allowed bilirubin increased to Total bilirubin ≤3.0 x ULN.
			6.2.1	Clarification added that if calculated GFR is <45mL/min, a protein/creatinine ratio can be used in 24 hours collected urine to confirm GFR ≥ 45 mL/min .
			8.5.7	Clarification added that no dose modifications are required for Grade 1 or transient peripheral neuropathy
			8.5.10	Updated guidance on dose modification in the case of biliary obstrutction.

			9.1	Note added that TNM version 8 should be used throughout the trial.
			9.3	Clarification added that the End of Cycle 4 scan for disease assessment can be performed from Cycle 4 Day 8 onwards.
			12.2.7	Events added to the list of exemptions from SAE reporting.
			17.2	For Central Review of Imaging, the recommended method of transfer of images will now be via the Image Exchange Portal / NHS Picture Archiving and Communication System.
			18.51	Futility analyses will be planned into this study.
			Throughout	Clarification added that Physical examination should be performed in addition to Weight and Vital signs (including pulse, blood pressure and temperature).