BILCAP

A randomised clinical trial evaluating adjuvant chemotherapy with capecitabine compared to expectant treatment alone following surgery for biliary tract cancer.

PROTOCOL

Version 8

11th Jul 2016

SPONSOR: The University of Southampton

COORDINATING CENTRE: Cancer Research UK Clinical Trials Unit, University of Birmingham

On behalf of the NCRI Upper GI Cancer Clinical Studies Group

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Sponsor: The University of Southampton

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AMENDMENTS:

The Following amendments and/or Administrative changes have been made to this protocol since the date of preparation

Amendment No.	Date of Amendment	Version No.	Type of amendment? (e.g. substantial/non-substantial/administrative change)
1	**28th Oct 2005**	**2**	Substantial amendment
2	**15th Sep 2006**	**3**	Substantial amendment
3	**16th Oct 2007**	**4**	Substantial amendment
4	**26th Aug 2008**	**5**	Substantial amendment
5	**23rd Apr 2009**	**6**	Substantial amendment
6	**6th Jan 2014**	**7**	Substantial amendment
8	**11th Jul 2016**	**8**	Substantial amendment

INVESTIGATOR SIGNATURE PAGE

BILCAP:
A randomised clinical trial evaluating adjuvant chemotherapy with capecitabine compared to expectant treatment alone following surgery for biliary tract cancer

Protocol Version 8, 11th Jul 2016

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I agree to adhere to the protocol as outlined and agree that any suggested changes to the protocol must be approved by the BILCAP Trial Management Group prior to seeking approval from the independent Ethics Committee

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), the Declaration of Helsinki, local regulations (as applicable) and the trial protocol and I agree to conduct the trial according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial

Investigators Signature _____

Printed name _____

Name of Institution _____

Date _____

The Principal Investigator should sign this page and submit a copy to the BILCAP Study Office

STUDY SUMMARY

Acronym: BILCAP

Title: A randomised clinical trial evaluating adjuvant chemotherapy with capecitabine compared to expectant treatment alone following surgery for biliary tract cancer.

Objectives: The primary objective is to compare length of survival of patients receiving adjuvant chemotherapy, compared to expectant treatment alone, following surgical resection of a biliary tract cancer. The secondary objectives are to compare adjuvant chemotherapy compared to expectant treatment in terms of 5-year survival rates, relapse free survival, toxicity, quality of life and health economics. The trial aims to recruit 410 patients.

Outcome Measures

Primary

- Survival (after 2 years follow-up)

Secondary

- Survival (after 5 years follow-up)
- Relapse free survival
- Toxicity
- Quality of life (QoL)
- Health economics

Population: Patients with resected biliary tract cancer

Main (but not exhaustive) inclusion criteria:

- Patients with histologically confirmed:
  - intrahepatic cholangiocarcinoma
  - extrahepatic/hilar cholangiocarcinoma
  - lower common bile duct cholangiocarcinoma
  - muscle invasive gallbladder cancer

  who have undergone a macroscopically complete resection with curative intent
- All patients should have had radical surgical treatment which includes liver resection pancreatic resection or, less commonly, both.
- ECOG Performance Status $\leq$ 2
- Adequate renal, haematological and liver function
- Age 18 years or over

Main (but not exhaustive) exclusion criteria:

- Pancreatic or ampullary cancer
- Mucosal gallbladder cancer
- Incomplete recovery from previous surgery or unresolved biliary tree obstruction
- Any previous chemotherapy or radiotherapy for biliary tract cancer

Treatment:

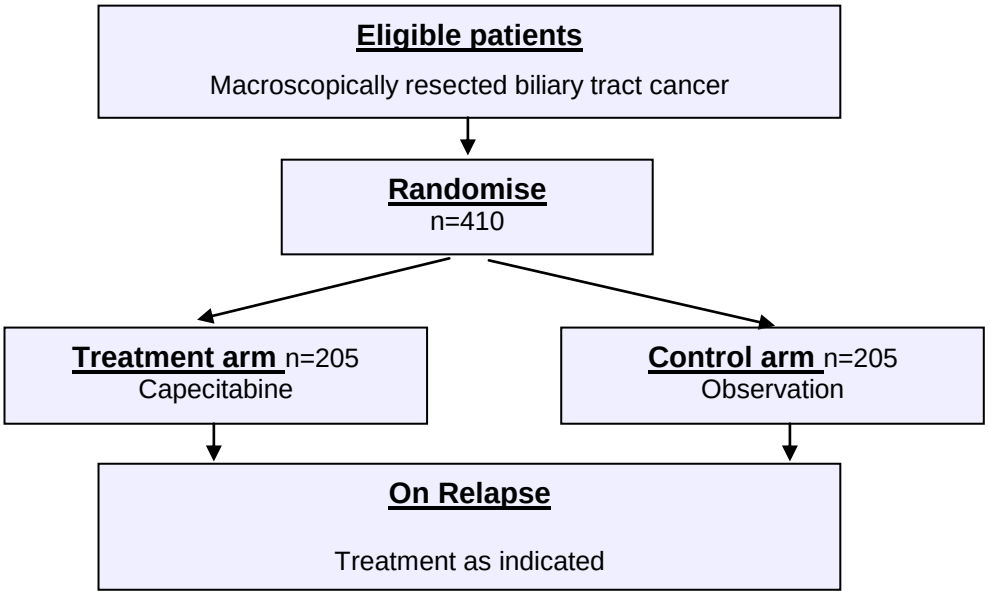
Treatment Arm - Post operative chemotherapy with capecitabine, 1250 mg/m^2 twice a day on day 1 to 14 of a 3 weekly cycle. Duration of treatment will be for a total of 24 weeks (8 cycles).

Control Arm - Observation (no scheduled post operative chemotherapy)

Duration:

The start date is March 2006 with accrual to be completed in 2014. Patients will be followed-up for 5 years.

TRIAL SCHEMA



Investigations required within 1 week prior to randomisation:

- Full blood count
- Serum creatinine, urea and electrolytes
- Liver function tests (including AST, ALP, Bilirubin)
- Ca19.9 measurement
- QoL questionnaire
- In addition baseline CT scan , or other adequate imaging confirmed by BILCAP office, should be performed within 4 weeks prior to surgery or within 12 weeks following surgery and before the start of treatment. If the treatment start date is >12 weeks, it will be necessary to contact the BILCAP Trial Office

National trial co-ordinator details:

Clive Stubbs BILCAP Trial Co-ordinator
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Tel: 0121 414 7671 Fax: 0121 414 2230 Email: BILCAP@trials.bham.ac.uk

Schedule of Clinical Assessments for Treatment & Control Arms

Assessments	Baseline [a] within 1 week prior to randomisation	Day 1 of every cycle *(Treatment Arm Only)*	End of treatment (within 4 weeks of last administered capecitabine) *(Treatment Arm Only)*	Follow-up post-randomisation 3 monthly (1st year)	Follow-up post-randomisation 6 monthly (2nd year)	Follow-up post-randomisation 12 monthly (3-5 years)
History	x					
Physical Examination	x	x	x	x	x	
Performance status	x	x	x	x	x	x
Weight	x	x	x	x	x	
Vital signs	x	x	x	x	x	
Haematology [c]	x	x [e]		x	x	
Biochemistry [d]	x	x [e]		x	x	
Ca19.9 measurement	x			x	x	x
CT Scan (chest, abdomen and pelvis)	x [b]			x [g] (at 6 and 12-month visits only)	x [g]	x [g]
Chemotherapy		x				
Toxicity / Adverse Event monitoring		x [f]	x			
Issue Patient Diary		x				
Quality of Life	x			x	x	
Symptom monitoring		x				

a Baseline assessments to be carried out within 1 week prior to randomisation, except:

b Baseline CT scan , or other adequate imaging confirmed by BILCAP office, should be performed within 4 weeks prior to surgery or within 12 weeks following surgery and before the start of treatment. If the treatment start date is >12 weeks, it will be necessary to contact the BILCAP Trial Office

c Haematology to include full blood count.

d Biochemistry to include liver function tests (AST, ALP, bilirubin), serum creatinine, urea and electrolytes.

e Haematology & biochemistry can be performed up to 5 days prior to day 1 of the treatment cycle.

f Toxicity monitoring not applicable on day 1 of the 1st cycle.

g Protocol CT scan schedule should be followed until disease recurrence is documented. After recurrence is documented CT scans to continue at Investigator's discretion and according to normal local practice.

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1 INTRODUCTION

1.1 Background

Biliary tract tumours are relatively rare, accounting for 0.7% of malignant tumours in adults, with approximately 1200 new cases registered each year in England and Wales (Cancer Survival Trends in England and Wales 1971 – 1995). The UK mortality rate is approximately 23 per million population (CRC Factsheet 1999;July). This grouping includes cholangiocarcinomas (both intra- and extra-hepatic), gallbladder carcinomas, and ampullary tumours in the following proportions:

Gallbladder	40%
Extra-hepatic cholangiocarcinoma	35%
Ampullary tumours	13%
Intra-hepatic cholangiocarcinoma	8%
Unspecified/other	4%

Cholesterol gallstones, obesity and increasing parity are the main risk factors for gallbladder carcinoma in Western populations (hence a 3:2 female to male preponderance). Other biliary tumours have an equal male to female ratio. Biliary tract cancer is becoming more common (Taylor-Robinson *et al*., 2001, Khan *et al*., 2002a). The incidence of cholangiocarcinoma is increasing substantially and it is now more common in the UK than hepatocellular carcinoma (Taylor-Robinson *et al*., 2001). The outlook remains poor. The 1-year and 5-year survival figures for adults diagnosed in England and Wales during 1986 – 1990 were 22% and 9% respectively (Cancer Survival Trends in England and Wales 1971 – 1995). Although some single centre publications suggest that good results may be obtained by surgery alone, the general experience of liver surgeons is poor, and that early relapse is the rule (Khan *et al*, 2002b).

Biliary tumours present the combined clinical problems of biliary obstruction and malignancy. Hepatic dysfunction can occur as a consequence of unrelieved biliary obstruction as well as local invasion of the vascular supply, but most patients die as a result of sepsis. This is usually consequent to inadequate biliary drainage and it is important in the management of these conditions that the combination of obstruction and infection should be prevented wherever possible (Ottow *et al*., 1985).

Most patients present with tumours that are too advanced for surgical resection. Unresectable cases are adequately palliated prior to further treatment (e.g. chemotherapy) either with or percutaneous or endoscopic stenting. Both plastic and metal stents may be used, although the frequent complications of blockage and infection must be monitored for and addressed promptly. In cases suitable for surgical resection preoperative drainage of the biliary tree is required in jaundiced patients. Here internal plastic stents are used where possible, although on occasions external drainage is necessary.

With respect to bile duct tumours, surgery to resect and reconstruct the biliary system (hepatico-jejunostomy) is only possible if the tumour is circumscribed and can be removed with tumour free margins on the bile duct, and sufficient functioning liver parenchyma to allow the patient to survive. The hepatic arterial and portal supply should normally be uninvolved although curative resection is still possible if vascular reconstruction is performed (Blumgart 1988). Survival appears to be enhanced when a liver resection is used (Lee *et al.,* 2000) perhaps by removing unexpected local extension into the adjacent liver segments. All patients with localised tumours should be discussed with a surgeon in a hepatobiliary unit. Gallbladder cancer may be resectable in the absence of distant metastases. Usually the resection involves segment IV and V of the liver and a radical lymphadenectomy. With more extensive liver involvement an extended right hepatic lobectomy may be performed. Excision of the bile duct may be performed where necessary.

Despite surgical resection, the prognosis remains dismal because of either local spread into the porta hepatis or metastatic disease. Survival after surgical resection varies widely between centres. However, resectability rates are generally low (Klempnauer *et al* 1997).

Fluoropyrimidine-based Chemotherapy in advanced biliary tract cancer

The place of radiotherapy or chemotherapy as adjuvant treatment following resection is uncertain**.** The majority of fluoropyrimidine-based (commonly 5-fluorouracil (5FU)) chemotherapy regimens have been used in the treatment of advanced biliary tract cancer (see Table 1.1).

As a single agent (modified by folinic acid) intravenous 5-FU has a response rate of 25-32%. The addition of cisplatin, doxorubicin, epirubicin, hydroxyurea or methotrexate appears to add little in terms of response rate. Prolonged 5-FU infusions with the addition of either cisplatin or interferon appear equally effective although these are relatively small phase II studies.

There is a paucity of randomised, phase III data. One study (Glimelius *et al.,*1996) randomised 90 patients (only 32 were patients with biliary cancer) to either best supportive care or best supportive care with 5-FU, etoposide and leucovorin (FELV) chemotherapy (although the etoposide was omitted for elderly patients because of the high incidence of mucositis). There was a statistically significant survival advantage from the chemotherapy arm in terms of survival (6 months vs. 2.5 months, p<0.01).

Table 1.1 Summary of fluoropyrimidine-based chemotherapy regimens

Author	Regimen	N	RR (%)	MS (mo)
Choi et al, 2000	5-FU 375 mg/m^2/d + LV 25 mg/m^2/d D1-5, q 28 d	28	32	6
Raderer et al, 1999	5-FU 400 mg/m^2 + LV 90 mg/d, D1-28 q35d	20	25	9.5
Patt et al, 1999	Cisplatin 80 mg/m^2, D1 + IFN 5MU, D1-4 + Doxorubicin 40 mg/m^2, D1 + CI-5-FU 500 mg/m^2/d, D1-3	41	35 (GB) 9 (chol)	
Ducreux et al, 1998	CI-5-FU 1000 mg/m^2, D1-5 + Cisplatin 100 mg/m^2, D2	25	24	
Comella et al, 1996	MTX 500 mg/m^2 , D1 + LFA 250 mg/m^2, D2 + 5-FU 600 mg/m^2 , D2, q14d		22	
Gebbia et al, 1996	LFA 100 mg/m^2 + 5-FU 600 mg/m^2 + oral hydroxyurea 1 g/m^2, weekly x6, q8/52	30	30	8
Patt et al, 1996	CI-5-FU 750 mg/m^2/d, D1-5 + IFN 5MU, D1,3,5; q14d	35	34	12
Kajanti et al, 1994	Epirubicin 20 mg/m^2 + MTX 150 mg/m^2 + 5-FU 600 mg/m^2 + LV rescue, weekly x3, q5-6/52	22	0	9
Smith et al, 1984	HAI-5-FU 1200mg/m^2/d, D1-4 + MMC 6mg/m^2, D1,4	11	64	12.5+

LV = leucovorin, IFN = interferon, CI = continuous infusion, MTX = methotrexate, LFA = levo-folinic acid, MU = mega units, MMC = mitomycin-C, RR = response rate, MS = median survival, GB = gallbladder, Chol = cholangiocarcinoma, HAI = hepatic arterial infusion

5-FU based adjuvant Chemotherapy in biliary tract cancer

There is only one phase III randomised controlled study to date for adjuvant treatment of patients with biliary tract cancer. This trial evaluated the effect of postoperative adjuvant therapy with mitomycin C (MMC) and 5-fluorouracil (5-FU) (MF arm) versus surgery alone (control arm) on survival and disease-free survival (DFS) for each specific disease, comprising resected pancreaticobiliary carcinoma separately (Takada *et al*., 2002). This trial revealed a significant survival benefit for patients with gallbladder cancer. However the trial was underpowered to show a survival advantage in cholangiocarcinoma and there was no significant survival

advantage for patients with biliary tract cancer overall. The chemotherapy regimen used in the trial was a chronic low-dose oral 5-FU, and it is not used in any standard treatment programme.

Oral 5-FU analogue studies.

The use of oral 5-FU analogues has been reported in a few studies (see table 2). Recent analogues have had very different results: **UFT** appears to have no efficacy in combination with leucovorin (response rate 0%), whilst **capecitabine** has fared better demonstrating the best results with gallbladder carcinoma patients (RR 50% and 100% 1-year survival). Confirmation of efficacy (response rate and survival data) from larger phase II and randomised phase III studies is awaited.

Table 1.2. Oral 5-FU analogue studies

Author	Regimen	N	RR (%)	MS (mo)
Lozano et al, 2000	Capecitabine 2000 mg/m^2/d, D1-14, q21d	37 HCC	13	67 (1-YS)
		18 Chol	6	60 (1-YS)
		8 GB	50	100 (1-YS)
Mani et al, 1999	UFT 300 mg/m^2/d + LV 90 mg/d, D1-28, q35d	13	0	6.5
Falkson et al, 1984	Oral 5-FU	53 GB	GB (biliary)	
	Oral 5-FU + STZ	34 biliary	11 (8)	
	Oral 5-FU + meCCNU		12 (0)	
			5 (17)	

LV = leucovorin, UFT = tegafur/uracil, STZ = streptozotocin, meCCNU = methyl-CCNU, RR = response rate, MS = median survival, 1-YS = 1-year survival, GB = gallbladder, Chol = cholangiocarcinoma

Other single chemotherapy agents

Other single agents have been tested in phase II studies. These include etoposide which showed no efficacy (Ekstrom et al., 1998). Intra-arterial mitomycin-C that appears effective in gallbladder carcinoma confined to the submucosa (48% response rate and 14-month median survival) (Kairaluoma *et al* 1988; Makela and Kairaluoma 1993).

Of the newer agents, Tomudex was shown to have limited efficacy (10% RR) in a mixed cohort of pancreatic (n=22) and biliary (n=8) cancers (Francois *et al* 2000) and in a single agent study of Irinotecan for gallbladder carcinomas, the study stopped recruiting biliary cancers due to

unacceptable toxicity (Alberts *et al* 2000). However, docetaxel was shown to be active and well tolerated on the basis of a 25% RR and 31% stabilisation of disease in a mixed group of gallbladder (n=13), cholangiocarcinomas (n=4) and ampullary tumours (n=3) (Agelaki *et al.,* 1999). Finally, there is relatively new interest in gemcitabine in biliary tract tumours, since it has been shown to be effective in the treatment of patients with advanced pancreatic cancer (Casper *et al.,* 1994; Rothenberg *et al.,* 1996; Storniolo *et al.,* 1997; Burris *et al*., 1997). The new interest means most of the reported studies are in abstract form (see Table 1.3) and there are no randomised data. To date there is no evidence that the response rate with this agent is better than that of a fluoropyrimidine (Raderer et al,1999).

Table 1.3 Gemcitabine-based studies

Author	Regimen	N	RR (%)	MS (mo)
Eckel et al, 2000	CI-Gemcitabine 100-150 mg/m^2/d, D1-21 q28d (MTD has been established at 100 mg/m^2/d)	15 panc. 9 biliary	N/A	
Dragovich et al, 2000	Gemcitabine 1500 mg/m^2, D1,8,15, q28d (at a limited rate of 10 mg/m^2/min)	13	8	
Gallardo et al, 2000	Gemcitabine 1000 mg/m^2, D1,8,15, q28d	25 GB	42	5.7
Weissmann et al, 1999	IA-Gemcitabine 1200 mg/m^2/d, D1-2, q28d	23 panc. 8 chol.	25	11+
Raderer et al, 1999	Gemcitabine 1200 mg/m^2, D1,8,15, q28d	19	16	6.5

CI = continuous infusion, MTD = maximum tolerated dose, IA = intra-arterial, RR = response rate, MS = median survival, GB = gallbladder, chol = cholangiocarcinoma.

1.2 Ongoing trials

In June 2009 the ABC-02 trial phase III study in advanced disease was presented and described a 3.4 month survival advantage from 8.3 to 11.7 months. Although this suggests that biliary tract cancer is a chemoresponsive disease, there are no studies examining the adjuvant treatment of biliary tract cancer apart from BILCAP.

1.3 Study Rationale

In summary, it remains unclear that adjuvant treatment of biliary tract cancer is of benefit, although one phase III trial suggests a benefit in a subset of patients with gallbladder cancer. Although fluoropyrimidine has shown poor response rates in advanced disease, the positive adjuvant data in bowel and pancreas suggest that in this setting a fluoropyrimidine may be the most appropriate agent.

We have considered the suitability of capecitabine as the investigational drug in this study. Although the data are limited, feasibility and compliance with treatment are critical in this study and so capecitabine has been accepted as the best option.

The study aims to evaluate capecitabine in patients who have undergone complete macroscopic resection for biliary tract cancer. The primary outcome measure will be length of survival and secondary outcome measures 5-year survival rates, relapse free survival, toxicity, Quality of Life (QoL) and health economics.

1.4 Concurrent Studies

The NCRN hepatocellular and biliary cancer studies provide a unique opportunity to assemble collaboration for a national tumour tissue bank with detailed clinical correlates. Because of the rarity of adequate fresh tissue collection in these relatively uncommon tumours, some of the participating centres in the NCRN studies may have an adequate infra-structure for fresh tissue collection, processing and storage as well as an interest in participating in a collaboration with an initial aim to prospectively collect 80-100 samples of each tumour type. Standard and uniform protocols will be used for collection, storage and processing for cDNA microarray analysis initially. If there are adequate centres interested, funding will be sought to extend this to functional proteomics, metabonomics, genomic analysis, as well as bioinformatics support. Initially, cDNA molecular profiles will be correlated to clinical datasets. Ideally clinical treatment response-driven analysis should be addressed, but this will be entirely dependant on the success of the degree of national collaboration, because of the difficulties in obtaining sequential samples of fresh tissue. Approval for analysis of hepatobiliary and pancreatic tumours (and correlation with clinical parameters) has been granted at University College London. The aim is to expand this to a more comprehensive material collection programme involving bile, blood, serum and tissue (see section 3.10 Trans-BILCAP).

2 STUDY OBJECTIVES

2.1 Primary objective

To determine whether adjuvant chemotherapy with capecitabine has any effect on length of survival compared to expectant treatment alone (observation), in patients who have undergone a macroscopically complete surgical resection of biliary tract cancer.

2.2 Secondary objectives

To assess:

(i) The effect of adjuvant capecitabine on 5-year survival rates

(ii) The effect of adjuvant capecitabine on relapse free survival

(iii) The toxicity associated with adjuvant capecitabine

(iv) The impact on quality of life (QoL) of capecitabine compared to observation

(v) The health economic aspects of adjuvant capecitabine compared to observation

3 STUDY DESIGN

3.1 Type of Study

This is a multicentre, prospective, randomised phase III trial of patients who have undergone a macroscopically complete surgical resection of a biliary tract cancer. Those patients who fulfil the inclusion criteria will be stratified by surgical centre, tumour site (hilar/extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, lower common bile duct cholangiocarcinoma and gall bladder carcinoma), and by the type of resection (RO/R1) and performance status (ECOG PS 0,1,2), and randomised to either:

Treatment arm: Capecitabine 1250 mg/m^2 given post-operatively twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles).

Control arm: No scheduled post-operative chemotherapy.

3.2 Recruitment

A total of 410 patients who have undergone a macroscopically complete surgical resection of a biliary tract cancer will be randomised equally into each arm of the study, and will be followed-up for 5 years.

3.3 Trial schema

3.4 Study treatment period

- The study treatment period begins on day one of the first cycle of capecitabine.
- End of the study treatment period is 4 weeks after the final cycle has been completed

3.5 Follow up period

Patients in the treatment and control arms will be followed up **for 5 years** after randomisation**.**

3.6 Definition of End of Trial

This trial consists of 2 phases: an interventional phase and a non-interventional phase. The definition of the **end of the trial** refers to the end of the interventional phase of the trial. This is defined as the date of the last protocol-specific follow-up visit of the last patient undergoing the trial.

Where a patient has completed the 5-year follow-up phase, the patient will be flagged with the office of national statistics (ONS) until death. Once the interventional phase of the trial has been

completed (as defined above), this long-term follow-up of patients by ONS flagging is classified as a non-interventional, long-term follow-up phase of the trial. The non-interventional phase of the trial is completed when the last patient enrolled in the trial has either died or has become lost to follow-up.

3.7 Source Data CRFs

Source data are defined as all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial. In the following cases the CRF will be considered the source document: - Quality of Life & Health Economics Questionnaire Booklets, and Capecitabine Patient diaries.

3.8 Quality of Life Sub-study

Quality of Life (QoL) is an important outcome, as standard measures of toxicity fail to account for perceived effects of treatment on patient well-being and health. Since progress in the acceptance of new treatments may be critically dependent on QoL consequences, all centres are required to participate in this aspect of the trial. However if patients do not wish to participate they can still take part in the BILCAP trial. All patients who consent to participating in the QoL study will be assessed using EORTC QoL questionnaire (QLQ-C30) version 3 with the EORTC QLQ-LMC21 site-specific add-on and EuroQoL (5 questions), (see Appendices 7 & 8). Although the QLQ-LMC21 has been designed for patients with colorectal liver metastases (Kavadas et al 2003) it contains most of the QoL scales and items that are pertinent to biliary tract cancer, and there are currently no available instruments specific to this subgroup of patients.

The QoL analysis will be in conjunction with Miss Jane Blazeby at the Department of Social Medicine, University of Bristol and Clinical Sciences at South Bristol. The main objective of QOL assessment within this trial is to determine how capecitabine impacts on QoL, and to examine differences between the two arms of the study. It is expected that during capecitabine treatment QoL may be diminished because of side effects of chemotherapy, and the site specific module is designed to detect these issues. It is also possible that because of better disease control patients randomised to the intervention arm may report better generic aspects of QoL such as fatigue and physical function.

3.9 Health Economics

The health economic evaluation will assess the relative cost effectiveness of the treatment regimes (chemotherapy or observation) for the duration of treatment and for the first two years of follow-up, using the same sub-set of QoL patients. An NHS (payor) perspective will be adopted, and cost effectiveness expressed in terms of incremental cost per Life Year (LY) and per QALY. Resource use data will be collected on the use of outpatient GP and Home services, extra drugs for support and use of inpatient hospital stay for treatment complications. Unit cost data will be collected from each centre and combined after analysis of differences. Total cost per patient will be estimated combining resource use with unit costs; the latter based on mean unit costs in the study and compared with national data (NHS Reference Costs and community health service costs).

The collection of the data for the economic evaluation will be a minimal additional burden to the patient as this data can be collected by adding the health problems questionnaire (5 questions – see Appendix 9) to the QOL booklet to ascertain the resource use, and a minimal burden to the clinician as the treatment data can be collected by additional questions added to the patient CRF forms filled out at each cycle of treatment. This has been demonstrated to be the most efficient way to collect these data.

The scope for validating data on resource use by use of routine NHS administrative system data will be explored, including obtaining patient consent. Modelling will be required to estimate the cost per life year and per QALY, for sensitivity analysis and also to explore the implications of generalising from the study. The health economic analysis will be in conjunction with Professor James Raftery and colleagues at the Wessex Institute for Health Research and Development (WIHRD) at the School of Medicine, University of Southampton, who have extensive experience in such work.

3.10 Trans- BILCAP Sub-study

The aim of Trans-BILCAP is to collect tissue blocks and blood from all BILCAP participants. The Trans-BILCAP sub-study is a unique opportunity to collect material for translational research of cancer of the biliary tract.

Trans-BILCAP Blood Sample Collection

Subject to participant consent prospective collection of a single blood sample (2 x 10 ml EDTA tubes) will be carried out. Please refer to the Blood Collection Guidelines within the Investigator Site File.

Trans-BILCAP Tumour and Normal Paraffin Block collection

Pairs of formalin-fixed paraffin embedded (FFPE) blocks containing either tumour or normal tissue will be collected for translational research for all patients who have not withdrawn their consent to participate in the BILCAP trial. Blocks for participants randomised into the BILCAP study have been stored in the hospital histopathology departments as per standard practice in the UK and these will be collected for research purposes. Consent will be obtained from surviving BILCAP clinical trial participants that met the eligibility criteria for the BILCAP study (unless the participants have withdrawn their consent to participate in the BILCAP study), to use their FFPE-blocks in research.

Blocks should be sent to the Cancer Sciences Tissue Bank in Southampton in accordance with the Trans-BILCAP Tissue Sample Collection Guidelines. Please be aware that it will be the responsibility of the local site research team to obtain their participant's pathology material if the material is stored at a separate site to the participating hospital.

It is appreciated that in some instances there may insufficient diagnostic material available for research purposes. If the local pathology team are concerned that there is insufficient tissue available for research, this should be communicated to the BILCAP Study Office.

The blocks will be retained at the Cancer Sciences Tissue Bank in Southampton for research purposes. The site research team may request the return of tumour blocks collected as part of the study at any time by submitting a request to the BILCAP Study Office.

The Human Tissue Act (HTA) code of practice sets out guidance to professionals carrying out activities which lie within the HTA remit. Establishments should follow the code of practice to ensure they meet the regulatory framework for removal, storage and use of 'relevant material' for research under the Human Tissue Act 2004 & Human Tissue (Scotland) Act 2006. In most cases the Acts require consent/ authorisation to be obtained for these purposes. Exceptions are provided for within the Act for instances where the tissue is used for a specific research project for which ethical approval has been sought from a recognised ethics committee and where the researcher is not in possession, and not likely to come into possession of information that identifies the person from whom the tissue has come.

The Medical Research Council (MRC) recognises that "samples can be stored for a long time, and may be of considerable value for research that was not, and could not have been envisaged at the time the material was obtained". They also recognise that "it is often not possible or not practicable to go back to the donors for new consent". The Human Tissue Act 2004 also recognises the value of tissue stored for diagnostic purposes as used for the advancement of the treatment of disease or human function.

In current practice, participant consent is sought at the outset to ensure informed consent is obtained for storing and using tissue for research purposes. However due to the historic context of the BILCAP clinical trial the tissue collection process was implemented after a large number of participants had been randomised into the trial. As a result of this a number of BILCAP participants have passed away before having an opportunity to provide consent to the tissue collection that is Trans-BILCAP. It is also felt that contacting relatives of participants for consent to use their tissue would have the potential to be significantly upsetting considering the historic nature of the trial. In the BILCAP clinical trial diagnostic tissue samples were obtained at surgery as standard routine care between 2006 and 2014.

Trans-BILCAP has been reviewed and approved by <insert ethics committee details and date of approval> additionally the researchers (laboratory staff, pathologists or researchers involved with the tissue collection) will not have access to the participants identifiable data nor will they have access to the clinical data related to participants tissue. The hospital site will retrieve the tissue samples from the NHS histopathology archives and will be requested to anonymise these before sending to Cancer Sciences Tissue Bank in Southampton. The Tissue Bank Manager will ensure that the tissue blocks are robustly anonymised and will assign a unique laboratory number only before sending on for analysis by the researcher. No participant identifiable data will be provided to the researchers nor will they have access to the clinical data, therefore they will not be able to link tissue sample analysis data with the participant's clinical outcome data.
The tissues will not be permanently or irrevocably unlinked, but the unique laboratory number will be used to prevent identification of the samples to the researchers involved.

4 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

- Patients with histologically confirmed biliary tract cancer (including intrahepatic cholangiocarcinoma, extrahepatic/hilar cholangiocarcinoma, muscle invasive gallbladder cancer or cancer of the distal bile duct who have undergone a macroscopically complete resection with curative intent.
- A radical surgical approach must have been employed which includes liver resection (see Appendix 1), pancreatic resection or less commonly both.
- Patients with pathological evidence of microscopic involvement of the margins of the excised specimen may be recruited as long as resection is macroscopically complete.
- ECOG Performance Status ≤ 2 (see Appendix 4)
- Age $\geq$ 18 years
- Adequate renal function:
  - serum urea and serum creatinine < 1.5 times upper limit of normal (ULN)
  - Calculated glomerular filtration rate (GFR) using Cockcroft-Gault $\geq$ 60 ml/min. If the calculated GFR is below 60 ml/min, isotope EDTA confirmation of adequate renal function (as detailed in the Summary of Product Characteristics (SPC) for capecitabine) is required (see Appendix 5)
- Adequate haematological function:
  - Haemoglobin $\geq$ 10g/dl
  - WBC $\geq 3.0 \times 10^9$/L
  - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq$ 100,000/mm^3
- Adequate liver function:
  - Total bilirubin $\leq 3 \times$ ULN
  - ALT or AST $\leq 5 \times$ ULN
  - Adequate surgical biliary drainage with no evidence of infection
- Women of child bearing age and child bearing potential MUST have a negative pregnancy test prior to study entry AND be using an adequate contraception method, which must be continued for at least 3 months after the study treatment has ended
- Effective contraception for male patients if there is a risk of conception, which must be continued for at least 3 months after the study treatment has ended
- Written informed consent
- Able to start treatment within 12 weeks of surgery. If the treatment start date is >12 weeks, it will be necessary to contact the BILCAP Trial Office

4.2 Exclusion Criteria

- Pancreatic or ampullary cancer
- Mucosal gallbladder cancer
- Incomplete recovery from previous surgery or unresolved biliary tree obstruction
- Use of other investigational agents during the study treatment period, or within 4 weeks of planned entry to the study
- History of other malignancy within 5 years of trial entry, except adequately treated cervical carcinoma-in-situ or non-melanotic skin cancer.
- Any previous chemotherapy or radiotherapy, given for biliary tract cancer.
- A serious co-existing medical condition likely to interfere with protocol treatment including a potential serious infection.
- Evidence of significant clinical disorder or laboratory finding which, in the opinion of the investigator, makes it undesirable for the patient to participate in the trial
- Psychological, familial, sociological or geographical factors considered likely to prevent compliance with the protocol.
- Any other serious uncontrolled medical conditions
- Pregnant or breastfeeding women

5 TREATMENT PLAN

5.1 Surgery

All patients should have had radical surgical treatment, as detailed in Appendix 1 and in the list of eligibility criteria (section 4), prior to entry into the study. All macroscopic disease must be removed and an attempt made to achieve microscopic clearance.

5.2 Drug Supply and Dispensing

Prescribing should be initiated by the investigator and a continued supply of drugs arranged according to normal local practice. Appropriate labelling requirements should be carried out, and full instructions are supplied in the Pharmacy File.

5.3 Protocol Treatment

Treatment Arm:

Once randomised to the treatment arm, chemotherapy should begin as soon as possible after surgery, and must begin within 12 weeks of surgery .

Patients should receive chemotherapy as follows.

- Capecitabine at the standard dose of 1250 mg/m^2 * given PO twice a day on day 1 to 14 of a 3 weekly cycle *
- Duration of treatment will be for a total of 24 weeks (8 cycles).
- Capecitabine tablets should be administered morning and evening and swallowed with water within 30 minutes after a meal.

* for dose calculation see Appendix 6

Control Arm:

No scheduled post operative treatment.

5.4 Clinical Procedures & Assessments

For details of clinical procedures and assessments to be carried out during treatment and follow up periods, see section 6.

5.5 Dose Reductions and Delays if Toxicity

All adverse experiences are to be graded according to the NCI-CTCAE grading system Version 3.0, a copy of which will be included in the Investigator Site Folder.

Dose reductions, treatment delays and discontinuation of treatment can be considered at the clinician's discretion, with reference to the Summary of Product Characteristics (SPC) for capecitabine (at http://emc.medicines.org.uk/**) and the guidelines below.**

For those toxicities considered by the investigator to be unlikely to become serious or life threatening and which do not result in a delay or interruption of therapy (e.g., alopecia, altered taste, etc) OR for any **grade I toxicities**, treatment will be continued at the original dosage, as determined at baseline, day 1.

If any grade 2, 3 or 4 toxicity occurs: there will be selective dose reduction depending on the following criteria:

Anaemia

All grades: no dose reduction, to be treated as clinically indicated.

Hand-Foot Syndrome

For **grades 2, 3 or 4:** dose reduction to be carried out according to **Table 5.1.**

Diarrhoea, Nausea, Vomiting

For **grade 2/3** diarrhoea, nausea, vomiting: (NB for **grade 4** see **Table 5.1**)

- Stop capecitabine and treat symptomatically (recommended use of Imodium [Loperamide] for diarrhoea).
- Restart at 100% of original dose if considered adequately controlled within 2 days of initiation of treatment.
- If control takes longer, then the dose should be modified according to **Table 5.1**

(NOTE: diarrhoea of > 2 days requires medical evaluation, including relevant diagnostic procedures, alternative treatment and possible investigation of DPD deficiency).

- If the adverse event recurs despite prophylaxis then dose modifications should also be made according to **Table 5.1.**

Liver Function

a) Drug-related Hyperbilirubinaemia

For drug related **grade 2/3/4** elevations in bilirubin:

- administration of capecitabine should be immediately interrupted until the hyperbilirubinaemia resolves or decreases in intensity or grade

Dose modifications should be managed according to **Table 5.1**

b) Liver Function Abnormalities Present at Baseline

Due to the commonly observed disruption to liver function, particularly intrahepatic cholestasis, associated with major hepatectomy, the trial inclusion criteria (see section 4.1) allow patients to enter the study with baseline liver function (total bilirubin or ALT/AST) equivalent to a Grade 2 adverse event (CTCAE v3.0).

For those patients for whom liver function on entry into the study (i.e. at baseline) is equivalent to a grade 2 adverse event, treatment should begin at standard dose and liver function should be monitored weekly. If liver function deteriorates to grade 3, dose delays and reductions should be managed as per Table 5.1 and the SPC (i.e. Interrupt treatment until resolved to grade 0 - 1, then continue at 75% of original dose).

All other toxicities

For all other grade 2, 3 or 4 toxicities, capecitabine dosage should be reduced as indicated in **Table 5.1.**

TABLE 5.1. Dose reductions and delays for toxicity

	GRADE 2*	GRADE 3	GRADE 4
1st appearance	Interrupt treatment until resolved to grade 0- 1, then continue capecitabine at original dose, with prophylaxis where possible	Interrupt treatment until resolved to grade 0- 1, then continue at 75% of original dose with prophylaxis where possible	Discontinue treatment, unless investigator considers it to be in the best interest of the patient to continue at 50% of the original dose, once toxicity has resolved to grade 0-1.
2nd appearance	Interrupt treatment until resolved to grade 0- 1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0- 1, then continue at 50% of original dose	Discontinue treatment
3rd appearance	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

Adverse events are to be graded according to the NCI-CTCAE grading system Version 3.0.

* If a patient experiences recurrent grade 2 toxicity at the end (last 4 days) of the 2 week treatment period, which resolves to grade 0-1 within the scheduled treatment-free rest period, the investigator can decide to continue at the same dose.

NOTE: For any event/toxicity that was apparent at baseline, the dose modifications will apply according to a corresponding shift in toxicity grading, if the investigator feels it is appropriate.

Once the dose of capecitabine has been reduced, it should not be increased at a later stage for any reason. For delays due to toxicity, if treatment is delayed for longer than 2 weeks then the patient will be considered "off treatment".

5.6 Biliary Tree Obstruction

The development of obstructive jaundice due to biliary tree obstruction in this setting usually heralds recurrent cancer. However in some instances it may be due to benign biliary obstruction. Appropriate measures will be undertaken to diagnose (e.g. by ultrasound and/or CT scan) and relieve the obstruction. Chemotherapy will be deferred until the Liver Function Tests have improved to the pre-treatment eligibility levels. Chemotherapy will then resume at the same time point it was interrupted if the cause is not malignant progression. In the event of recurrence of the disease, study chemotherapy in the treatment arm will stop.

5.7 Anti-Emetics

Anti-emetics will be given to patients in the treatment arm if required. Generally, capecitabine is not highly emetogenic and does not require routine anti-emetic dosage.

5.8 Concomitant Medication

Patients may receive all concomitant therapy deemed to provide adequate supportive care at the Investigator's discretion. All such medications or other treatments taken by the patient during the study (including those initiated prior to the start of the study) will be recorded in the patient's clinical notes, and patient case report forms (CRFs). However, the use of other experimental drugs is not permitted within 28 days of completion of the study treatment period.

5.9 Contraindications

For details of contraindications, Investigators should refer to the Summary of Product Characteristics (SPC) for Capecitabine (at http://emc.medicines.org.uk/).

5.10 Discontinuation of Treatment

A patient should discontinue study treatment in the event of any of the following:

- due to a toxicity as described in Section 5.5, Table 5.1, or the SPC for capecitabine.
- development of a life-threatening toxicity
- due to a treatment delay due to toxicity of longer than 2 weeks (see section 5.5)
- if relapse is documented
- administration of any other anti-tumour chemotherapy, radiotherapy or investigational agent during the study treatment period.
- pregnancy
- any other reason given by the investigator
- patient decides to discontinue study treatment
- patient withdraws consent to participate in trial (see Section 10.6)

Full details of the reasons for discontinuation or withdrawal of the trial drug should be recorded on the relevant CRF if clinician-initiated. If it is the patient's decision a simple statement reflecting patient preference will suffice.

All patients, including those who were withdrawn from trial treatment, should be followed-up in accordance with the protocol, unless the patient has withdrawn their consent. In this case no more data will be gathered on the patient; however all information up until the patient's retraction of consent will be used.

5.11 Compliance

Compliance with study treatment is critical in this study. To measure compliance, patients will be issued with a Capecitabine Patient Diary at the start of each treatment cycle. Patients will be asked to complete the diary, recording the time that each dose was taken, and whether any doses were missed. The diary also includes a section where the patient can record any relevant information such as side effects suffered or reasons for missed doses. The completed diary for each cycle will be collected by the centre and returned to the BILCAP Study Office along with the treatment CRF.

6 PROCEDURES & CLINICAL ASSESSMENTS

6.1 Schedule of Events

Patient monitoring, blood tests, clinical and radiological assessments will be conducted as defined in the charts below. Assessments are described in more detail in the following sections.

Table 6.1 Schedule of Events for Treatment Arm

	TREATMENT ARM					
	Baseline [a] within 1 week prior to randomisation	**Day 1 of every cycle**	**End of treatment** (within 4 weeks of last administered capecitabine)	**Follow-up post-randomisation 3 monthly (1st year)**	**Follow-up post-randomisation 6 monthly (2nd year)**	**Follow-up post-randomisation 12 monthly (3-5 years)**
History	x					
Physical Examination	x	x	x	x	x	
Performance status	x	x	x	x	x	x
Weight	x	x	x	x	x	
Vital signs	x	x	x	x	x	
Haematology [c]	x	x [e]		x	x	
Biochemistry [d]	x	x [e]		x	x	
Ca19.9 measurement	x			x	x	x
CT Scan (chest, abdomen and pelvis)	x [b]			x [g] (at 6 and 12-month visits only)	x [g]	x [g]
Chemotherapy		x				
Issue Patient Diary		x				
Toxicity/Adverse Event monitoring		x [f]	x			
Quality of Life	x			x	x	
Symptom monitoring		x				

a Baseline assessments to be carried out within 1 week prior to randomisation, except:

b Baseline CT scan , or other adequate imaging confirmed by BILCAP office, should be performed within 4 weeks prior to surgery or within 12 weeks following surgery and before the start of treatment. If treatment start date is >12 weeks, it will be necessary to contact the BILCAP Trial Office.

c Haematology to include full blood count.

d Biochemistry to include liver function tests (AST, ALP, bilirubin), serum creatinine, urea and electrolytes.

e Haematology & biochemistry can be performed up to 5 days prior to day 1 of the treatment cycle.

f Toxicity monitoring not applicable on day 1 of the 1st cycle.

g Protocol CT scan schedule should be followed until disease recurrence is documented. After recurrence is documented CT scans to continue at Investigator's discretion and according to normal local practice.

Table 6.2 Schedule of Events for Control Arm

	CONTROL ARM			
	Baseline [a] Within 1 week prior to randomisation	**Follow-up post-randomisation** **3 monthly (1st year)**	**Follow-up post-randomisation** **6 monthly (2nd year)**	**Follow-up post-randomisation** **12-monthly (3-5 years)**
History	x			
Physical Examination	x	x	x	
Performance status	x	x	x	x
Weight	x	x	x	
Vital signs	x	x	x	
Haematology [c]	x	x	x	
Biochemistry [d]	x	x	x	
Ca19.9 measurement	x	x	x	x
CT Scan (chest, abdomen and pelvis)	x [b]	x [e] (at 6 and 12-month visits only)	x [e]	x [e]
Chemotherapy				
Issue Patient Diary				
Toxicity / Adverse Event monitoring				
Quality of Life	x	x	x	
Symptom monitoring				

a Baseline assessments are to be carried out within 1 week prior to randomisation, except:

b Baseline CT scan, or other adequate imaging confirmed by BILCAP office, should be performed within 4 weeks prior to surgery or within 12 weeks following surgery and before the start of treatment. If treatment start date is >12 weeks, it will be necessary to contact the BILCAP Trial Office.

c Haematology to include full blood count.

d Biochemistry to include liver function tests (AST, ALP, bilirubin), serum creatinine, urea and electrolytes.

e Protocol CT scan schedule should be followed until disease recurrence is documented. After recurrence is documented CT scans to continue at Investigator's discretion and according to normal local practice.

6.2 Baseline Assessments

Baseline evaluations should be carried out for all patients within 1 week prior to randomisation as outlined below:

- **History**
- **Physical examination, weight, vital signs and assessment of ECOG performance status ***
- **Full blood count ***
- **Biochemistry *** (including serum creatinine, urea & electrolytes)
- **Liver function tests *** (including AST, ALP, Bilirubin)
- **Ca19.9 measurement**
- **QOL assessment**

In addition, all patients must have a baseline **CT scan of the chest abdomen and pelvis** (performed within 4 weeks prior to surgery or within 12 weeks after surgery, and before the start of treatment).

If a baseline CT scan is not available, but adequate imaging can be demonstrated to the BILCAP trial office, that the patient may be eligible. This will be treated on a case by case basis by the BILCAP trial office and the patient may proceed if the demonstrated level of imaging is approved.

* Baseline ECOG PS, full blood count, biochemistry and liver function tests must meet eligibility criteria for study entry as specified in Section 4.1.

6.3 Assessments During Treatment

The following will be performed on **day 1 of every cycle** (unless otherwise stated) for **patients in the treatment arm:**

- **Physical examination, weight, vital signs and assessment of ECOG performance status**
- **Full blood count ***
- **Biochemistry** (including serum creatinine, urea & electrolytes) *
- **Liver function tests** (including AST, ALP, Bilirubin) *
- **Toxicity & Adverse Event monitoring for the preceding cycle** - worst grade toxicity (according to NCI-CTCAE version 3.0 criteria) will be recorded on the appropriate pages of the patient case report forms)
- **Symptom monitoring**
- **Issue of Capecitabine Patient Diary (and collection of diary for previous cycle)**.

* Full blood count, biochemistry & liver function tests can be performed up to 5 days prior to day 1 of the treatment cycle. Dose delays/reductions for each cycle should be managed according to Section 5.5. of the protocol (i.e. at the Investigators discretion, with reference to the SPC for capecitabine at http://emc.medicines.org.uk/ and the guidelines given in section 5.5)

6.4 End of Treatment Assessments

The following will be performed after the final treatment cycle or on discontinuation of treatment:

- **Physical examination, weight, vital signs and assessment of ECOG performance status** (to be performed within 4 weeks of last administration of capecitabine).
- **Toxicity & Adverse Event monitoring for the final cycle** - (worst grade toxicity for the 4 weeks following the last administration of capecitabine will be recorded on the appropriate pages of the patient CRF for the final cycle).
- **Collection of Capecitabine Patient Diary for the final cycle**

6.5 Follow-Up Assessments

For post-randomisation follow-up, patients in **both the treatment and control arms** will have **Ca19.9 measurement** and clinical review (including **physical examination, weight, vital signs** and **assessment of ECOG performance status, haematology & biochemistry**):

- Every 3 months for the first year
- Every 6 months for the second year

In addition all patients will have a **CT scan of the chest, abdomen and pelvis:**

- Every 6 months for the first 2 years

After this 2 year follow-up period, all patients will then have **Ca19.9 measurement, assessment of Performance Status, and a CT scan of the chest, abdomen and pelvis:**

- Every 12 months up to 5 years

NOTE: "Additional scans may be carried out at the Investigator's discretion". The protocol CT scan schedule should be followed until disease recurrence is documented. After recurrence is documented, CT scans should continue at the Investigator's discretion and according to normal local practice

For the first 5 years post-randomisation, all patients will be followed up as indicated above. However patients should also still be followed up as is routine practice at each centre. After the 5 year period, all patients should be followed up until death, according to routine practice. All patients will be flagged at the Office of National statistics (ONS).

6.6 Guidelines for Management in the Event of Disease Recurrence

Patients in either arm who develop recurrent disease may be treated at the discretion of the investigator. The patients may be offered chemotherapy including recruitment into the trial ABC02.

6.7 Quality of Life Assessment

A named person at each participating centre must be nominated to take responsibility for the administration, collection and checking of QoL questionnaires. The QoL questionnaires (and the BILCAP health problems questionnaire – see below) will be collated into a QoL & Health Economics booklet to be given to patients to complete. The questionnaire booklet will be handed out to the patient by the Investigator or study nurse at the hospital /clinic.

Once the patient has consented to participate in the trial, the first QoL assessment will be taken **prior to randomisation**. After this, QoL assessments will be taken at **each follow-up visit during the first 2 years of follow-up** (or for as long as the patient remains well enough to attend the clinic).

There are 3 versions of the QoL & Health Economics booklets (a, b & c), to be completed as follows:

- **Version a (baseline):** to be completed by patients prior to randomisation
- **Version b (follow-up during first year)**: to be completed by patients at each 3-monthly follow up visit during the first year (i.e. at 3, 6, 9 & 12 month post-randomisation)
- **Version c (follow-up during second year):** to be completed by patients at each 6-monthly follow-up visit during the second year (i.e. at 18 & 24 months post-randomisation)

The patient will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire booklet is approximately 15-20 minutes.

6.8 Health Care Economics Assessment

The treatment arm and control arm are expected to differ in costs. Additional information on supportive care, including additional treatment, will be recorded on patient case report forms

(CRFs). The BILCAP health problems questionnaire (included in the QoL booklet, see above) will be used for additional health care evaluation.

7 SAFETY REPORTING & MONITORING

7.1 Adverse Events Definitions

Adverse Event (AE): any untoward medical occurrence in a patient receiving treatment according to the study protocol and which does not necessarily have a causal relationship with the protocol treatment.

Adverse Reaction (AR): all untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered. *An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction (UAR): an AR, the nature or severity of which is not consistent with the applicable product information (i.e. the Summary of Product Characteristics (SPC) for capecitabine which is a licensed product). *When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected*.

Serious Adverse Event (SAE) or **Serious Adverse Reaction (SAR)**:
Any untoward medical occurrence or effect that at any dose :

- Results in death*
- Is life-threatening**
- Results in persistent or significant disability/incapacity
- Requires hospitalisation or prolongation of existing hospitalisation***
- Is a congenital anomaly/birth defect discovered during the study period
- Is a new primary cancer

Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. An AE or AR that is not immediately life threatening or does not result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above (excluding cancer), should be considered serious.

* Except death due to biliary tract cancer

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

*** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for a pre-existing

condition, including elective procedures, which has not worsened does not constitute a serious adverse event.

Suspected Unexpected Serious Adverse Reaction (SUSAR): a SAR that is unexpected i.e. the nature or severity of the event is not consistent with the applicable product information (i.e. the SPC for capecitabine). A SUSAR should meet the definition of an AR, UAR and SAR as detailed above.

7.2 Assessment of Adverse Events

All adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for adverse events (NCI CTCAE version 3.0), a copy of which will be enclosed in the Site Folder, and causality (relationship to study therapy) will be assessed. Adverse events incurred but not categorised by the NCI CTCAE should be graded by the physician and recorded using a scale of (1) mild, (2) moderate, or (3) severe on the CRF. A pre-existing condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event-reporting period.

It is the responsibility of the local Investigator to assess seriousness and causality to protocol treatment when reporting an SAE. The Clinical Co-ordinator (or Deputy) will also be responsible for independently determining the seriousness, causality and expectedness of the event.

Causality Criteria:

Relationship	**Description**
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is *little* evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after study treatment). There is *another reasonable explanation* for the event (e.g., the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is *some* evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the study treatment). However, the influence of *other factors may have contributed* to the event (e.g., the patient's clinical condition, other concomitant events).
PROBABLE	There *is evidence* to suggest a causal relationship, and the influence of other factors is *unlikely*.
DEFINITE	There is *clear* evidence to suggest a causal relationship, and other possible contributing factors can be *ruled out*.

7.3 Adverse Events Monitoring & Reporting Period

All adverse events will be assessed by the Investigator and recorded onto the appropriate pages of the patient case report forms (CRFs). New **toxicities** in the Treatment Arm will be recorded for four weeks after the last administration of capecitabine or until the start of other anti-cancer treatment, whichever occurs first.

All **Serious Adverse Events (SAEs)** occurring in both the Treatment Arm and Control Arm will be recorded for at least **9 months post randomisation**, and for at least **4 weeks after the last administration of capecitabine** (if applicable), or until the start of other anti-cancer treatment, whichever occurs first. The Investigator will take all therapeutic measures necessary for resolution of any adverse event. Any medication necessary for treatment of the adverse event must be recorded onto the concomitant medications section of the patient CRF. If more that one adverse event occurs, each event should be recorded separately.

7.4 Serious Adverse Event Reporting

For patients in both the Treatment Arm and Control Arm:

All SAEs occurring during the **first 9 months post-randomisation**, and for **at least 4 weeks after the last administration of capecitabine** (if applicable), even if not thought to be related to protocol treatment, must be reported in an expedited manner to the BILCAP Study Office using the SAE form supplied in the site folder, as outlined below:

In the case of an SAE the Investigator must immediately (within 24 hours of awareness of event):

- **Complete** an SAE Form. This should be signed by a relevant member of the site trial team.
- **Send by fax** the signed and dated SAE Form to the **BILCAP Study Office,** along with the fax cover sheet provided in the site folder:
    - **Fax (24 Hours) 0121 414 2230**
    - (alternative fax number: 0121 414 3700)

- A receipt of the SAE form should be faxed back to the centre within 2 working days. Telephone the BILCAP Study Office to inform the Trial Co-ordinator if a fax is not received ☎: **0121 414 7671**
- **Telephone on day of awareness** the BILCAP study office **if SAE is life-threatening or fatal ☎: 0121 414 7671**
- **Notify** LREC and the NHS Trust as required by local policy (there is no requirement to report SAEs to LREC unless this is part of local policy).

It is the responsibility of the sponsor or designee to report all Suspected Unexpected Serious Adverse Reactions (SUSARS) as determined by the Clinical Co-ordinator (or deputy) to the relevant regulatory authorities (e.g. Medicines and Healthcare products Regulatory Agency (MHRA) and the Multi-Centre Research Ethics Committee (MREC)) in the expedited time frame required by UK legislation. All Investigators will be notified of SUSARS on a regular basis. The BILCAP Study Office will send a safety report to the MHRA and MREC annually.

7.5 Follow-up of Adverse Events

In the case of an SAE, the subject must be followed up until recovery is complete in terms of clinical and laboratory parameters, or until the event has stabilised. Follow up may continue after completion of protocol treatment if necessary. Follow-up information on any SAE will be documented using the SAE Form and sent to the BILCAP Study Office.

7.6 Expected Adverse Reactions

The common toxicities of capecitabine are plantar/palmar erythema (57%), diarrhea (47%), nausea (35%), stomatitis (23%), vomiting (18%), fatigue (16%), abdominal pain (11%), asthenia (10%) and myelosuppression. Less common toxicities are detailed on the product Summary of Product Characteristics (SPC) at http://emc.medicines.org.uk/.

8 OUTCOME MEASURES

8.1 Primary outcome measure

Length of survival: Survival will be calculated from the time of randomisation to the date of death (from any cause) or censor date (date last seen alive). All patients will be followed up for at least 2 years for this primary analysis.

8.2 Secondary outcome measures

5-year survival rates: Survival will be calculated from the time of randomisation to the date of death (from any cause) or censor date (date last seen alive). All patients will be followed up for at least 5 years for this secondary analysis.

Relapse free survival: Disease recurrence will be assessed during the first 5 years after randomisation. Relapse-free survival is defined as the time between the date of randomisation and the date of documented disease recurrence (if this occurs within 5 years) or disease related death.

Toxicity in the treatment arm will be analysed in terms of the incidence, severity, type, causality and duration.

Quality of Life (QoL) will be assessed using EORTC QOL Questionnaire (QLQ-C30 version 3) with the EORTC QLQ-LMC21 site-specific add-on, and EuroQoL (5 questions).

Health care economics will be assessed using the BILCAP health problems questionnaire as well as additional data on required supportive care from the treatment and follow-up forms.

9 STATISTICAL CONSIDERATIONS

9.1 Randomisation & Stratification

Participating oncology or surgical centres will randomise patients into the trial. A 1:1 treatment randomisation will be performed. Treatment will not be blinded. Patients will be stratified by surgical centre, tumour site (hilar/extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, lower common bile duct cholangiocarcinoma or gall bladder carcinoma) and by the type of resection (RO/RI) and performance status (ECOG PS 0,1,2).

9.2 Sample Size

The primary outcome measure is overall survival with sample size calculations based on comparison of two-year rates. The two-year survival rates achieved in the control arms of the one phase III trial in biliary tract cancer is around 20% (Takada et al 2002). The aim of this trial is to increase this to 32% using capecitabine. In order to detect this 12% increase with a 2-sided significance level of 5% and 80% power, 360 patients will need to be randomised into the trial. This would require 135 deaths in either treatment arm.

The data reviewed during the DMC meeting of July 2013 indicated that 2-year survival in the control arm is not as hypothesised at the design stage. On consultation with the IDSMC and TSC it was agreed that the recruitment target be increased to 410 patients. It is expected that this goal will be met in July 2014 and the required event rate (270 deaths in total) will be achieved one year later, in July 2015. This is the earliest time at which the TMG predicts sufficient statistical power will be obtained, although, continued assessment of recruitment is required. Note that the hazard ratio (0.71) and error rates of the original design are maintained.

Since the 12% difference is optimistic we will endeavour to detect smaller differences of 10% if recruitment exceeds expectation. A sample size of 520 patients is required to detect a 10% absolute survival difference based on a 2-year survival of 20% (i.e. detection of 10% absolute survival differences of 20%-30%) at the 5% level of significance with an 80% power. Whilst this is larger than the original estimate, it satisfies the primary and secondary endpoints. This would require 190 deaths in either treatment arm. Also in the event that the control group exceeds expectation, 520 patients would also allow the detection of 12% differences if the 2 year survival rate for the control group is anything between 20% to 40%. This will be a decision for the IDSMC.

9.3 Analysis

The primary analysis will be comparison of overall survival across treatment groups, calculated from the time of randomisation to the date of death (or censor date). All analysis will be on an intention to treat basis. Comparison of survival estimates will be by log-rank analysis. Toxicity and response rates will be compared across treatment groups using Pearson's chi-square test. QoL scores will be calculated according to the EORTC C30 manual and EuroQoL guidelines and compared across treatment groups using standardised area under the curve analyses and Mann-Whitney tests. Cox proportional hazards models will be undertaken to determine prognostic factors and their influence on survival and provide an adjusted treatment effect by important prognostic and stratification factors.

9.4 Interim Analyses

The only interim analyses will be for the Independent Data and Safety Monitoring Committee (IDSMC) who will review the data 6 months after the first patient is recruited into the trial or after the first 30 patients are recruited, which ever is sooner. It will then meet at approximately annual intervals or more frequently as required. The IDSMC will also decide whether to increase the sample size to detect a 10% absolute survival difference based on a 2-year survival of 20%.

The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data based on accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC) as to the continuation of the trial. Depending on the success of recruitment into the trial the IDSMC will also review whether to increase the sample size to detect a 10% absolute survival difference based on a 2-year survival of 20%.

9.5 Milestones

The study will be adopted by the National Cancer Research Network. We aim to recruit 410 patients by July 2014. Follow-up will continue until death or withdrawal from study for any other reason. All patients (including those withdrawn from study) will be followed up by ONS (Office of National Statistics) flagging, which will provide copies of patient's death certificates. The planned initiation date was October 2005. However the trial actually opened to recruitment at the first

centre in March 2006. The planned completion of enrolment is July 2014 and planned study completion 2019.

March 2006:	trial open to recruitment
30 recruited or 6 months after 1st recruited (whichever sooner):	1st report to IDSMC
Annually thereafter (more frequently if required):	report to IDSMC
410 recruited (planned 2014) :	close trial to recruitment
Minimum of 1 year after trial closed to recruitment	final analysis of 2 year survival
Minimum of 5 years after trial closed to recruitment	final analysis

10 STUDY PROCEDURES

10.1 Pre-randomisation (Baseline) Evaluations

Pre-randomisation evaluations should be carried out as outlined in Section 6.2 The inclusion and exclusion criteria will be checked at the registration telephone call. Patients will be randomised prior to treatment and treatment allocations will be given during the call.

10.2 Randomisation Procedures

Patients satisfying the entry criteria of the study will be randomised into the study. The Trials Centre will then send confirmation of the patient's inclusion in the trial and the treatment allocation and patient trial number.

To randomise a patient the investigator should:

- **Obtain** patient's written informed consent to participate in the study
- **Complete** the Randomisation Form
- **Contact** the CRCTU in Birmingham by telephone.

  ☎: 0800 731 7625 or 0800 371 969 (9am- 5pm Monday to Friday)

  Fax: 0800 328 6412 (24 hours)
- **Record** in the patient's notes, patient details: - unique patient trial number allocated & treatment allocation.
- **Send** a copy of the Patient Consent Form **by post** to the BILCAP study office
- **Send** the original Randomisation Form **by post** to the BILCAP study office (with extra details added e.g. trial number, treatment allocation).
- **Send** the patient's GP a letter indicating their participation in the study.
- **File** the original Patient Consent Form in the Investigator Site Folder
- **File** copies of the Randomisation Form, randomisation confirmation report & GP Letter in the Investigator Site Folder
- **Enter patients details into Enrolment Log**

10.3 Study Start-Up and Core Documents

Centres wanting to participate in the study should contact the **BILCAP Study Office** to obtain information. The principal investigator at each centre must ensure that the protocol has site specific approval (SSA) by the relevant Local Research Ethics Committee (LREC) and should provide the study office with the following core documentation, and attend an initiation visit or teleconference/telephone call before the site becomes activated:

- The site contact details
- Clinical Study Site Agreement signed by principal investigator at the centre & R&D/Trust
- A current signed and dated copy of each participating investigator's CV
- Site responsibilities sheet with signatures
- The R&D/Trust approval letter
- Application for SSA

10.4 Forms and Data Collection

All study data will be recorded on the case report forms (CRFs) provided. The CRFs must be completed and signed by the Investigator, or designee, as soon as the requested information is available and the CRF pages returned promptly to the **BILCAP Study Office**. In all cases it remains the responsibility of the Investigator for the timing, completeness, legibility and accuracy of the Case Report Forms and he/she will retain a copy of each completed form and each QoL booklet and capecitabine patient diary. The investigator will supply the study office with any required background data from such records. Data reported on the CRFs should be consistent with the source data in the medical notes, or the discrepancies should be explained.

Entries should be made in ballpoint pen on the CRFs provided in black or blue ink and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator or designee. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used.

10.5 Archiving

To enable peer review and/or audits from Health Authorities, the Investigator must agree to keep records, including the Investigator Site File, the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent

forms, copies of all CRFs, QoL booklets and Capecitabine Patient Diaries, records of drug dispensing and assessments such as CT scans All essential source and study documentation must be securely retained by the Investigator, for at least 5 years after the completion of the trial and the Investigator must seek prior permission from the sponsor if the centre decides to destroy such documents after the requisite period of 5 years for their retention, as defined in the Clinical Study Site Agreement.

10.6 Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason. The Investigator also has the right to withdraw patients from the study. Full details of the reasons for withdrawal should be recorded on the relevant CRF if clinician-initiated; otherwise a simple statement reflecting patient preference will suffice.

NOTE: Patients who discontinue study treatment, but who have not withdrawn their consent to participate in the trial, should still be followed-up in accordance with the protocol.

11 STUDY ORGANISATION

11.1 Trial Management

The **Trial Development Group** consists of the Chief Investigator, Clinical Co-ordinator, and other collaborators (as listed at the front of the protocol) as well as the Trial Co-ordinator, statisticians and other trials staff at the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham.

The **Trial Management Group (TMG)** includes the Chief Investigator, Clinical Co-ordinator & Deputies, Trial Statistician, Trial Co-ordinator and other trials staff at the CRCTU. This group will report to regular meetings of the NCRI Upper GI Clinical Studies Group. Access to data arising from this trial will be governed by the TMG. The TMG will be responsible for amending the study protocol as required.

The **Trial Steering Committee (TSC)** will consist of three independent members, as well as the Chief Investigator, Clinical Co-ordinator and trial statistician. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The TSC will be responsible for monitoring study progress, reviewing amendments to the study protocol if

required, overseeing the trial conduct and providing information to the IDSMC. The ultimate decision for the continuation of the trial lies with the TSC.

BILCAP will be co-ordinated by the Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer Studies, University of Birmingham, UK. The CRCTU is responsible for the day-to-day running of the study, centre initiation, monitoring, reporting to the TSC and IDSMC, analysis, and presentation of results.

11.2 Indemnity

This is a clinician-initiated and clinician-led study with a grant provided by Cancer Research UK. All clinicians and Research Nurses working on the study will have NHS indemnity provided as per local guidelines. In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available in the event of clinical negligence being proven. There are no special arrangements for compensation made in respect of any serious adverse events occurring though participation in the study, whether from the side effects listed, or others yet unforeseen. The manufacturer, supplier or importers of the medicinal product have strict liability for the product under UK law.

The University of Southampton will act as the sponsor. The University of Southampton has in force a Clinical Trials insurance providing cover for legal liabilities, including negligent harm to participants, arising from their participation in and Sponsorship of, this trial. The trial will be co-ordinated by the CRCTU, University of Birmingham. The University of Birmingham has in force a Public Liability Policy and/or Clinical Trials Policy which provides cover for 'negligent harm' and the activities here are within that coverage. No provision has been made by the University of Birmingham for indemnity in the event of a claim for non-negligent harm.

11.3 Site Responsibilities

Prior to entering patients, Investigators should have sent all the required registration documents to the Trials Centre. Local Research Ethics Committee (LREC) Site specific approval (SSA) and Trust R&D approval are mandatory and the relevant local staff (Co-investigators, data managers, research nurses, pharmacists etc) should be identified and have received information about the trial.

The Principal Investigator at each participating centre has overall responsibility for the study and all patients entered into the study at that centre, but may delegate responsibility to other

members of the study team as appropriate. The Principal Investigator must ensure that all staff involved are adequately trained and their duties have been logged on the Site Responsibilities & Signatures Sheet.

11.4 Protocol Compliance and Monitoring

BILCAP is being conducted under the auspices of the Cancer Research UK according to the current guidelines for Good Clinical Practice. Participating centres will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights, as detailed in the Declaration of Helsinki. Participating centres will be monitored by checking incoming forms for compliance with the protocol, consistent data, missing data and timing. Study staff will be in regular contact with centre personnel (by phone/fax/email/letter) to check on progress and deal with any queries they may have. On site monitoring will also be undertaken. Monitoring will be carried out according to the CRCTU Monitoring Policy and the appropriate level of monitoring will be reviewed on an ongoing basis and modified accordingly. Centres may be suspended from further recruitment in the event of serious and persistent non-compliance.

12 ETHICAL AND REGULATORY STANDARDS

12.1 Regulatory Status

This trial will be carried out under a Clinical Trial Authorisation (CTA), and SUSAR's and SAR's will be reported to the regulatory authorities in accordance with EU Directive 2001/20/EC and UK legislation.

12.2 Ethical Conduct of the Study

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments. Copies of the declaration may be obtained by contacting the CRCTU, or from the WMA website: http://www.wma.net/e/policy/17-c_e.html

The protocol will be approved by a Multi-Centre Research Ethics Committee (MREC). Before entering patients into the study, the principal investigator at each centre must ensure that the protocol has the approval of the relevant Local Research Ethics Committee (LREC).

The **BILCAP Study Office** will send an annual trial progress report to the MREC and will send an annual safety report to the MHRA and MREC. All Investigators will be notified of SUSARs on a regular basis.

12.3 Patient Informed Consent

It is the responsibility of the Investigator to obtain written informed consent in compliance with national requirements from each patient prior to entering the trial.

The patient information sheet and consent form will be available in electronic format from the BILCAP Study Office, to enable individual centres to print these onto their headed paper. The patient should be given ample time to read the patient information sheet and the opportunity to inquire about details of the trial. They should also be given time to discuss their participation with others outside of the clinical trials team e.g. family, friends, GP. Patients should also be given another opportunity to ask the clinician and the research nurse questions regarding their participation in the trial. All questions or concerns about the trial should be answered to the satisfaction of the patient.

If the patient still wants to participate in the trial, the patient and Clinician should both sign and date the latest version of the Patient Consent Form (printed on the centres headed paper). If a patient is unable to sign the consent form, an impartial witness should be present during the entire informed consent discussion and should sign the form once the patient has indicated their consent.

12.4 Patient Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. At randomisation, with the patient's consent, the patients name will be collected to allow flagging with the Office of National Statistics. To preserve patient confidentiality, only their initials, date of birth, hospital number and trial number will be recorded on case report forms (CRFs) after the patient has been randomised into the study. The Investigator must ensure the patient's confidentiality is maintained and must maintain documents not for submission to the trials unit (e.g. patients' written consent forms) in strict confidence.

The Trials Office will preserve the confidentiality of patients taking part in the study and is registered under the data protection act (DPA Z6195856). Information will be securely stored at the BILCAP Trials Office on paper and electronically in an encoded format, and will be accessible only by authorised personnel. The Trials Office will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients should be reassured that their confidentiality will be respected at all times.

With the patient's consent, their GP will be informed that they are taking part in the trial and may be asked to provide information from the patient's records if required for the study. Access to patients' medical records may be required by authorised members of the research team, to enable them to retrieve or validate information needed for the study. The confidentiality of the medical records will be respected at all times. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

12.5 Protocol Amendments

Any variation in procedure from that specified in the **BILCAP** protocol may lead to the results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be submitted in writing to the **BILCAP Study Office** to be pre-approved by the TMG. All agreed protocol amendments will be documented by the CRCTU and will be submitted to the MREC/MHRA for approval prior to circulation to all centres. Changes not pre-approved by the TMG will be considered as protocol deviations. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interests of individual patients.

13 PUBLICATION AND INTELLECTUAL PROPERTY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group. Members of the Trial Management Group will be listed as authors and other significant contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Surgeons and Oncologists at the highest recruiting centres will also be acknowledged.

Participating centres may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. Ownership of intellectual property resulting from the

trial will be governed in accordance with the Co-ordinating Centre Agreement, Clinical Study Site Agreements and the CRUK terms and conditions for research grants and awards.

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APPENDIX 1: SURGERY

All patients should have had radical surgical treatment. All macroscopic disease must be removed and an attempt made to achieve microscopic clearance.

- In the case of intrahepatic bile duct cancer, surgery should take the form of a radical liver resection.
- With extrahepatic/hilar cholangiocarcinoma, a liver resection, usually in the form of a hepatectomy (sometimes extended) should be performed together with segment I resection and a radical lymphadenectomy extending at least to the hepatic artery territory.
- With muscle invasive gallbladder cancer, a resection of segments IV and V should be performed and an extended R hepatectomy advised in cases with 10 mm or more liver invasion. A radical lymphadenectomy as described above should be performed. The bile duct may be removed if required for oncological reasons.
- In the event of a laparoscopic cholecystectomy having been performed for an undiagnosed gallbladder cancer, in addition to a liver resection the port sites should where possible be excised.
- Patients with gallbladder cancer which has not extended to involve the muscle layers or lymph nodes are not eligible for recruitment to the trial.
- In the case of cancer of the distal bile duct a Whipples procedure should be performed.

APPENDIX 2: SUMMARY OF AJCC CATEGORIES FOR TNM CLINICAL STAGING

Primary Tumour (T)

Intrahepatic Bile Ducts
TX - Primary tumour cannot be assessed
T0 - No evidence of primary tumour
T1 - Solitary tumour without vascular invasion
T2 - Solitary tumour with vascular invasion; or multiple tumours none more than 5 cm
T3 - Multiple tumours more than 5 cm or tumour involving a major branch of the portal or hepatic vein(s)
T4 - Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Gallbladder
TX - Primary tumour cannot be assessed
T0 - No evidence of primary tumour
T1 - Tumour invades lamina propria or muscle layer
  T1a - tumour invades lamina propria
  T1b - tumour invades muscle layer
T2 - Tumour invades perimuscular connective tissue; (no extension beyond serosa or into liver)
T3 - Tumour perforates serosa and/or invades the liver and/or one other adjacent organ or structure
T4 - Tumour invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures

Hilar & Extrahepatic Bile Ducts
TX - Primary tumour cannot be assessed
T0 - No evidence of primary tumour
T1 - Tumour confined to bile duct histologically
T2 - Tumour invades beyond wall of bile duct
T3 - Tumour invades liver, gallbladder, pancreas, and/or unilateral branches of portal vein or hepatic artery
T4 - Tumour invades main portal vein or branches bilaterally, common hepatic artery, or other structures

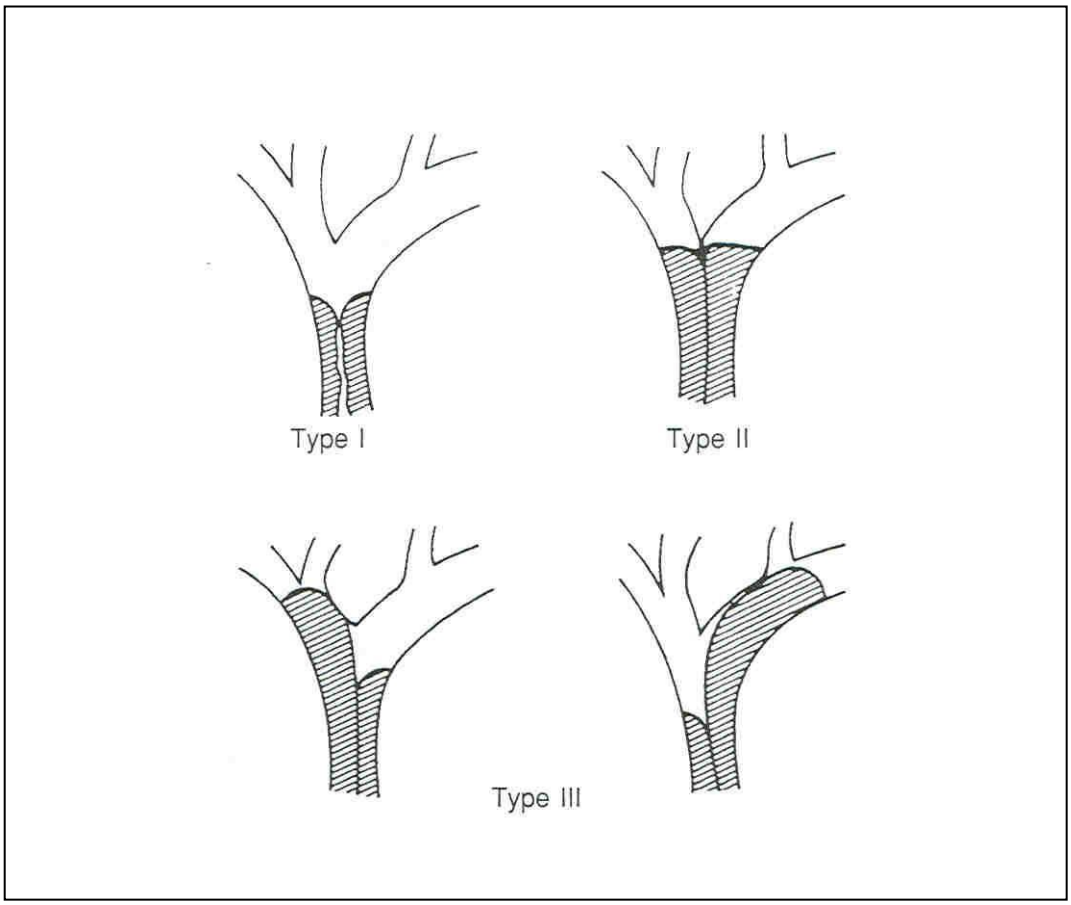
Regional Lymph Nodes (N)

NX - Regional lymph nodes cannot be assessed
N0 - No regional lymph node metastasis
N1 - Regional lymph node metastasis

Distant Metastasis (M)

MX - Distant metastasis cannot be assessed
M0 - No distant metastasis
M1 - Distant metastasis

APPENDIX 3: BISMUTH-CORLETTE CLASSIFICATION SCHEME OF BILIARY STRUCTURES



APPENDIX 4: ECOG SCALE OF PERFORMANCE STATUS

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

References:

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

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

APPENDIX 5: RENAL FUNCTION

Calculated creatinine clearance (Cockroft Gault formula)

24-hour urine collections are frequently unreliable and a calculated creatinine clearance using the Cockcroft Gault formula is all that is required in most cases. If the calculated GFR is < 60 ml/min use isotope EDTA clearance to confirm adequate renal function *:

$$\text{GFR} = \frac{A \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

where A = 1.25 (male) and 1.05 (female)

* (as detailed in the Summary of Product Characteristics (SPC) for Capecitabine at http://emc.medicines.org.uk/)

APPENDIX 6: CALCULATION OF DOSES.

The following table for dose calculations, taken from the Summary of Product Characteristics (SPC) for Capecitabine at http://emc.medicines.org.uk/, is provided for reference.

Capecitabine Dose Calculations

Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine of 1250 mg/m^2

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose 1250 mg/m^2	**Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)**		**Reduced dose (75%) 950 mg/m^2**	**Reduced dose (50%) 625 mg/m^2**
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	1300
≥ 2.19	2800	2	5	2150	1450

APPENDIX 7: EORTC QLC-C30 & QLC-LMC21 QOL QUESTIONNAIRRES

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – LMC21

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

During the past week :	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had trouble with eating?	1	2	3	4
32. Have you felt full up too quickly after beginning to eat?	1	2	3	4
33. Have you worried about losing weight?	1	2	3	4
34. Have you had problems with your sense of taste?	1	2	3	4
35. Have you had a dry mouth?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you been less active than you would like to be?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had pain in your stomach area?	1	2	3	4
40. Have you had discomfort in your stomach area?	1	2	3	4
41. Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
42. Have you had pain in your back?	1	2	3	4
43. Have you felt slowed down?	1	2	3	4
44. Have you felt lacking in energy?	1	2	3	4
45. Have you had trouble having social contact with friends?	1	2	3	4
46. Have you had trouble talking about your feelings to your family or friends?	1	2	3	4
47. Have you felt stressed?	1	2	3	4
48. Have you felt less able to enjoy yourself?	1	2	3	4
49. Have you worried about your health in the future?	1	2	3	4
50. Were you worried about your family in the future?	1	2	3	4
During the past four weeks:				
51. Has the disease or treatment affected your sex life (for the worse)?	1	2	3	4

APPENDIX 8: EQ-5D QOL QUESTIONNAIRRE

EQ - 5D

Health Questionnaire

(English version for the UK)
(validated for use in Eire)

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

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

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

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

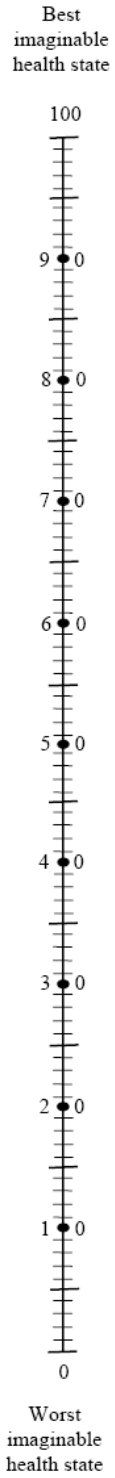
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

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

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

Your own health state today



APPENDIX 9: BILCAP HEALTH PROBLEMS QUESTIONNAIRE

Section 4: BILCAP Health Problems Questionnaire

To be filled out by patients prior to randomisation:

Since you were discharged from hospital after your surgery, we would like you to tell us about any health problems you may have had. Please answer all the questions yourself by ticking the box that best applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) Since you were discharged after your surgery, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ **(if no, go straight to question 2)**

If Yes:

b) How many times did you talk to a doctor in this time? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor:

1 a GP (i.e. a family doctor), ☐
2 a specialist, ☐
3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐
2 at your home, ☐
3 in the doctor's surgery, ☐
4 at a health centre, ☐
5 or elsewhere? ☐

f) Did the doctor prescribe you any medication?

Yes ☐ No ☐

If yes, was this prescribed for use over a short period or permanently?

Short ☐ Permanently ☐

Please list the prescribed medication below:

_____

_____

Please go on to the next page ⟶

2. Hospital visits
Since you were discharged from hospital after your surgery have you had any visits to hospital for any reason?

Yes ☐ No ☐ **(if no, please go to question 3)**

If yes, please give details of your attendance or admittance?
1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. Since you were discharged from hospital has a nurse visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 4)**

If yes, how many times? _____

4. Since you were discharged from hospital has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 5)**

If yes, how many times? _____

5. Since you were discharged from hospital has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 5, what was the problem?

_____

_____

_____

_____

THANK YOU VERY MUCH FOR COMPLETING THESE QUESTIONS.

Section 4: BILCAP Health Problems Questionnaire

For patients on follow up during the first year

During the last three months (i.e. since you last filled out this questionnaire), we would like you to tell us about any health problems you may have had. Please answer all the questions yourself by ticking the box that best applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) During the last three months ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ **(if no, go straight to question 2)**

If Yes:

b) How many times did you talk to a doctor in these three months? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor:

1 a GP (i.e. a family doctor), ☐
2 a specialist, ☐
3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐
2 at your home, ☐
3 in the doctor's surgery, ☐
4 at a health centre, ☐
5 or elsewhere? ☐

f) Did the doctor prescribe you any medication?

Yes ☐ No ☐

If yes, was this prescribed for use over a short period or permanently?

Short ☐ Permanently ☐

Please list the prescribed medication below:

_____

_____

Please go on to the next page ⟶

2. Hospital visits
During the last three months have you had any visits to hospital for any reason?

Yes ☐ No ☐ **(if no, please go to question 3)**

If yes, please give details of your attendance or admittance?
1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 3 months has a nurse visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 4)**

If yes, how many times? _____

4. During the last 3 months has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 5)**

If yes, how many times? _____

5. During the last 3 months has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 5, what was the problem?

_____

_____

_____

_____

_____

THANK YOU VERY MUCH FOR COMPLETING THESE QUESTIONS.

Section 4: BILCAP Health Problems Questionnaire

For patients on follow up during the second year

During the last six months (i.e. since your last visit to hospital for follow-up), we would like you to tell us about any health problems you may have had. Please answer all the questions yourself by ticking the box that best applies to you.

THE INFORMATION YOU PROVIDE WILL BE KEPT STRICTLY CONFIDENTIAL AND USED ONLY FOR MEDICAL RESEARCH.

1. Talking to a doctor

a) During the last six months ending yesterday, apart from any visit to a hospital, did you talk to a doctor, either in person or by telephone?

Yes ☐ No ☐ **(if no, go straight to question 2)**

If Yes:

b) How many times did you talk to a doctor in these six months? (please circle)

1 2 3 4 5 6 7 8 9 or more

c) Was this consultation

under the National Health Service, ☐ or paid for privately? ☐

d) Was the doctor:

1 a GP (i.e. a family doctor), ☐
2 a specialist, ☐
3 some other kind of doctor? ☐

e) Did you talk to the doctor

1 by telephone, ☐
2 at your home, ☐
3 in the doctor's surgery, ☐
4 at a health centre, ☐
5 or elsewhere? ☐

f) Did the doctor prescribe you any medication?

Yes ☐ No ☐

If yes, was this prescribed for use over a short period or permanently?

Short ☐ Permanently ☐

Please list the prescribed medication below:

_____

_____

Please go on to the next page ⟶

2. Hospital visits
During the last six months have you had any visits to hospital for any reason?

Yes ☐ No ☐ **(if no, please go to question 3)**

If yes, please give details of your attendance or admittance?
1. Out-patient; ☐ how many times _____
2. In patient; ☐ how many days _____
3. Casualty; ☐ how many days _____

3. During the last 6 months has a nurse visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 4)**

If yes, how many times? _____

4. During the last 6 months has anyone from social services or a voluntary organisation visited you at your home for any reason?

Yes ☐ No ☐ **(if no, please go to question 5)**

If yes, how many times? _____

5. During the last 6 months has a relative or friend taken time off work to look after you?

Yes ☐ No ☐

If yes, how many days? _____

If yes to any of the above questions 1 - 5, what was the problem?

_____

_____

_____

_____

_____

THANK YOU VERY MUCH FOR COMPLETING THESE QUESTIONS.

APPENDIX 10: BILCAP CAPECITABINE PATIENT DIARY

Dear Patient,

Please use this sheet to keep a record of your capecitabine (Xeloda) tablets as you take them. You will be taking capecitabine tablets twice a day (morning and evening) for 14 days, followed by a gap of 7 days with no capecitabine.

Each dose of ..... **mg** is made up from: ..... **x 500 mg tablet(s)**

..... **x 150 mg tablet(s)**

Swallow the tablets with water within 30 minutes after the end of a meal. Please record the time that you take each dose. If you miss a dose, record this by writing "missed" on the sheet. Do not take the missed dose at all and do not double the next one. Instead continue with your standard dosing schedule and check with your doctor.

If you develop diarrhoea or any other severe side-effect it may be necessary to stop taking the capecitabine tablets. Please phone your 24-hour telephone advice number if this happens.

Date: (nurse to complete)	**Day:**	**Morning Dose:** please record time taken	**Evening Dose:** please record time taken
___ / ___ / ___	1	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	2	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	3	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	4	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	5	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	6	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	7	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	8	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	9	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	10	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	11	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	12	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	13	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	14	_____ : _____ am	_____ : _____ pm
___ / ___ / ___	15	_____ : _____ am	
___ / ___ / ___ to ___ / ___ / ___		**No capecitabine tablets taken on these days**	

Additional Notes: (e.g. please note any side effects or any reasons for missing a dose)

THANK YOU FOR TAKING THE TIME TO COMPLETE THIS DIARY.

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