CONFIDENTIAL

ESPAC - 4

EUROPEAN STUDY GROUP FOR PANCREATIC CANCER - TRIAL 4.

Combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers.

National Cancer Research Institute (NCRI)

Study co-sponsors:

The Royal Liverpool and Broadgreen University Hospitals NHS Trust
Prescot Street
Liverpool
L7 8XP
UK

The University of Liverpool
Research and Business Services
The Foresight Centre
3 Brownlow Street
Liverpool
L69 3GL
UK

EudraCT Number: 2007-004299-38
ISRCTN Number: ISRCTN96397434
MREC Number: 08/H1005/1

Protocol Version: 9
Date: 7th January 2014

CANCER RESEARCH UK

LCTU Liverpool Cancer Trials Unit

Table of Contents

1. List of Abbreviations and Definition of Terms

Abbreviation	Abbreviated Term	Abbreviation	Abbreviated Term
AE	Adverse Event	**l**	Litre
BP	Blood Pressure	**LFTs**	Liver Function Tests
BSA	Body Surface Area	**LREC**	Local Ethical Research Committee
CA19-9	Cancer Antigen 19-9	**LCTU**	Liverpool Cancer Trials Unit
CI	Chief Investigator	**mg**	Milligram
CRF	Case Report Form	**MHRA**	Medicines and Healthcare Products Regulatory Agency
CRP	C-reactive protein	**min**	Minute
CR-UK	Cancer Research United Kingdom	**ml**	Millilitre
CTAAC	Clinical Trials Advisory & Awards Committee	**MRC**	Medical Research Council
CTCAE	Common Toxicity Criteria for Adverse Events	**MREC**	Main Research Ethics Committee
CV	Curriculum Vitae	**NCI**	National Cancer Institute
DSUR	Development Safety Update Report	**NCRI**	National Cancer Research Institute
ECOG	Eastern Co-operative Oncology Group	**NHS**	National Health Service
EORTC	European Organisation for Research and Treatment of Cancer	**NICE**	National Institute for Clinical Excellence
ESPAC	European Study group for Pancreatic Cancer	**NRES**	National Research Ethics Service
EU	European Union	**PT**	Prothrombin Time
GCP	Good Clinical Practice	**QA**	Quality Assurance
GemCap	Clinical study comparing Gemcitabine and Capecitabine in advanced ca pancreas	**QC**	Quality Control
GMP	Good Manufacturing Practice	**QLQ**	Quality of Life Questionnaire
ICH	International Conference on Harmonisation	**R&D**	Research and Development
ISDMC	Independent Data and Safety Monitoring Committee	**SAE**	Serious Adverse Event
IEC	Independent Ethics Committee	**SOP**	Standard Operating Procedure
INR	International Normalized Ratio	**SUSAR**	Suspected Unexpected Serious Adverse Reaction
IRAS	Integrated Research Applications System	**ULN**	Upper Limit of Normal
IV	Intravenous	**UK**	United Kingdom

2. Study Protocol Approval

I, the undersigned, hereby approve and authorise this clinical study protocol:

Signature: _____ **Date:** 13/JAN/2014

Prof. John Neoptolemos – Chief Investigator
The Owen and Ellen Evans Chair of Cancer Studies
Director, CR-UK Liverpool Cancer Trials Unit
C Block, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Signature: _____ **Date:** 17/JAN/2014

Signed on behalf of the University of Liverpool (Co-Sponsor)
Alexander Astor
Head of Research Support
Research Support Office
University of Liverpool
Block D, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Signature: _____ **Date:** 16/1/14

Signed on behalf of the Royal Liverpool and Broadgreen University Hospitals NHS Trust (Co-Sponsor)
Professor Tom Walley
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Research and Development
4th Floor, Linda McCartney Centre
Prescot Street
Liverpool
L7 8XP

This protocol has been approved by:

- The Chief Investigator
- The ESPAC Working Group/Internal Project Team
- The National Cancer Research Institute

3. Protocol Statements

This document describes the ESPAC-4 trial and provides information about the procedures for entering patients into it. The protocol should not be used as aide memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections and amendments may be necessary. These will be circulated to the enlisted copy holders and investigators registered in the trial. Clinical problems relating to the trial should be referred to the Chief Investigator or Co-investigator via the Liverpool Cancer Trials Unit (LCTU).

3.1. Statement of Compliance

This study will be conducted in compliance with the protocol, Liverpool Cancer Trials Unit (LCTU) Standard Operating Procedures (SOPs), Research Governance Framework for Health and Social Care, the International Conference for Harmonisation (ICH) Guideline to Good Clinical Practice (GCP), the European Union (EU) Directive 2001/20/EC; transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and the European Union (EU) Directive 2005/28/EC; transposed into UK Law as the UK Statutory Instrument 2006 No 1928.

3.2. Registration of Study

This study has been granted National Research Ethics Service (NRES) approval and holds a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). Each centre must undergo Site Specific Assessment by the relevant Research and Development department) and must be granted approval from the Trust where the trial will be carried out. Each participating centre and Principal Investigator must be approved by the MREC and MHRA either on the original application or by submission of a substantial amendment.

4. Protocol Synopsis

Investigational Medicinal Products: Gemcitabine, Capecitabine

Title of Study: EUROPEAN STUDY GROUP FOR PANCREATIC CANCER –TRIAL 4. Combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers.

Study Design: A phase III, two arm, open-label, multi-centre randomised clinical trial comparing combination gemcitabine and capecitabine therapy with gemcitabine alone

Chief Investigator: Professor John Neoptolemos

Number of Sites: Approximately 120 centres in approximately 8 countries.

Study Period: The first patient was randomised in November 2008. For the two year final analysis survival the last patient, last visit is planned for November 2016. Last patient last visit of the trial is planned for November 2019.

Main Objective(s): To investigate if combination chemotherapy (gemcitabine and capecitabine), when used as adjuvant therapy in patients following resection for pancreatic ductal adenocarcinoma or peri-ampullary carcinoma, improves survival over adjuvant therapy using gemcitabine alone.

Methodology: This study is designed as a phase III, two arm, open-label, multicentre, randomised clinical trial comparing combination gemcitabine and capecitabine with gemcitabine alone when used as adjuvant therapy following resection for pancreatic ductal adenocarcinoma or peri-ampullary carcinoma.

Patients will be randomised within 12 weeks of undergoing 'curative' surgery and will receive 24 weeks of chemotherapy. Chemotherapy must start within 2 weeks of the date of randomisation. All patients will be followed up from randomisation every 3 months for a minimum of 5 years and ideally until death.
Patients will be randomised equally between the two arms:

1. Gemcitabine alone.
2. Gemcitabine and Capecitabine.

Patients will be stratified by:

- Resection margin status
- Country

Translational study: The translational element of the trial will involve the collection and storage of frozen tissue, formalin fixed paraffin embedded tissue, blood cell, serum, plasma and urine samples. The aim of the study is to identify an expression profile in tumours associated with good or poor response to capecitabine or gemcitabine, allowing correlation with somatic and germline genetic features facilitating development of a practical molecular response signature. Analysis of key enzymes and nucleoside transporters involved in gemcitabine and capecitabine metabolism and uptake (including polymorphisms) will be performed.

Collection of samples from patients prior to adjuvant chemotherapy:
The following samples will be taken on the morning of surgery, again post-surgery prior to receiving chemotherapy and at the first 3 month follow up visit.

- Urine sample: 50ml of mid flow urine being stored immediately after sampling at -80 degrees Celsius;
- Blood samples: approximately 9ml of blood will be taken in (KE/9ml)/(K2E) tube (Sarstedt Monovette/Vacutainer) for plasma and cells and (Z/ 7.5ml)/(CAT) tube (Sarstedt Monovette/Vacutainer) for serum. Plasma will be separated from cells following approved protocols and the cells plasma and serum will be stored at -80 degrees Celsius.

The following samples will be taken during surgery.

- Tissue samples: trucut biopsies will be frozen in liquid nitrogen in theatre following approved SOPs; subsequent to pathological analysis sections will be frozen in local pathology departments (again following approved SOPs) and paraffin embedded blocks prepared and sections H&E stained for preliminary characterisation of the blocks.

Patients will be retrospectively grouped according to survival after surgery. RNA extracted from tumours will be used to challenge arrays. Gene expression and sample classification profiles will be examined by correspondence analysis.

Number of Patients to be Enrolled:

A) 722 pancreatic ductal adenocarcinoma patients (480 expected events) are to be randomised in total, 328 in each arm of the study

and

B) 740 peri-ampullary carcinoma patients (404 expected events) are to be randomised in total, 370 in each arm of the study.

N.B. UK sites will not recruit *Extrahepatic bile ducts - distal (ICD-O C24.0)* or *Small intestine (ICD-O C17)* tumour patients into the peri-ampullary cohort; these patients will be recruited only from non-UK centres.

Main Criteria for Inclusion:

1. A) Patients who have undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection).
   or
   B) Patients who have undergone complete macroscopic resection for peri-ampullary carcinoma (R0 or R1 resection).
2. Completion of all pre-operative investigations.
3. Histological confirmation of the primary diagnosis.
4. Histological examination of all resection margins.
5. Patients randomised ideally within 12 weeks of surgery, although case by case the CI will consider patients up to 14 weeks, and can begin treatment ideally within 14 weeks of surgery.
6. No evidence of malignant ascites, liver metastasis, spread to other distant abdominal organs, peritoneal metastasis, spread to extra-abdominal organs – CT (chest, abdomen, pelvis) scan within 3 months prior to randomisation.
7. A WHO performance status ≤ 2
8. Creatinine clearance $\geq$ 50ml/min (according to Cockcroft and Gault or equivalent value following local practice).
9. Fully recovered from the operation and fit to take part in the trial.
10. Able to attend for administration of the adjuvant therapy.
11. Able to attend for long-term follow-up.
12. Life expectancy > 3 months.
13. No previous or concurrent malignancy diagnoses (except curatively-treated basal cell carcinoma of skin, carcinoma in situ of cervix).
14. No serious medical or psychological condition precluding adjuvant treatment.
15. Fully informed written consent given.

Main Criteria for Exclusion:

1. Use of neo-adjuvant chemotherapy or other concomitant chemotherapy.
2. Patients with pancreatic lymphoma.
3. Macroscopically remaining tumour (R2 resection).
4. Patients with TNM Stage IV disease.
5. Patients younger than 18 years.
6. Pregnancy.
7. New York Heart Association Classification Grade III or IV.
8. Previous chemotherapy.
9. All men or women of reproductive potential, unless using at least two contraceptive precautions, one of which must be a condom.
10. Patients with known malabsorption.
11. Patients with a baseline neutrophil count of $<1.5 \times 10^9$/l.
12. Patients with a baseline platelet count of $<100 \times 10^9$/l.
13. Patients with severe hepatic impairment.

Duration of Treatment: Arm 1: Gemcitabine will be administered once a week for three weeks out of every four weeks (one cycle) for six cycles, i.e. 24 weeks.

Arm 2: Gemcitabine will be administered on day 1, 8 and 15. Capecitabine will be administered orally for 21 days followed by 7 days' rest. Treatment will be repeated every 4 weeks for a total of 24 weeks.

Primary Outcome: Pancreatic Ductal Adenocarcinoma: Length of survival.

Peri-Ampullary Carcinoma: Length of survival.

Secondary Outcomes: Pancreatic Ductal Adenocarcinoma:

1. Toxicity
2. Quality of life (assessed using the EORTC QLQ-C30 v3)
3. Two year survival
4. Five year survival
5. Relapse free survival (RFS)

Peri-Ampullary Carcinoma:

1. Toxicity
2. Quality of life
3. Four year survival
4. Relapse free survival (RFS)

Statistical Methods: Analysis of overall survival (time of randomisation to the time of death from any cause or the censor date) and relapse free survival (time of randomisation to the time of relapse or the censor date) will be carried out using a logrank analysis, and Cox proportional hazards modelling, or alternative, will be used to investigate and adjust any treatment effect by stratification factors and prognostic factors.

The proportion of grade 3/4 toxicity will be compared across treatments using Pearson's chi-square test with continuity correction or Fishers Exact test. Quality of life will be assessed over time and treatment groups compared using longitudinal analysis. Joint modelling or quality-adjusted survival analysis will be undertaken to allow a simultaneous assessment of quality of life and survival.

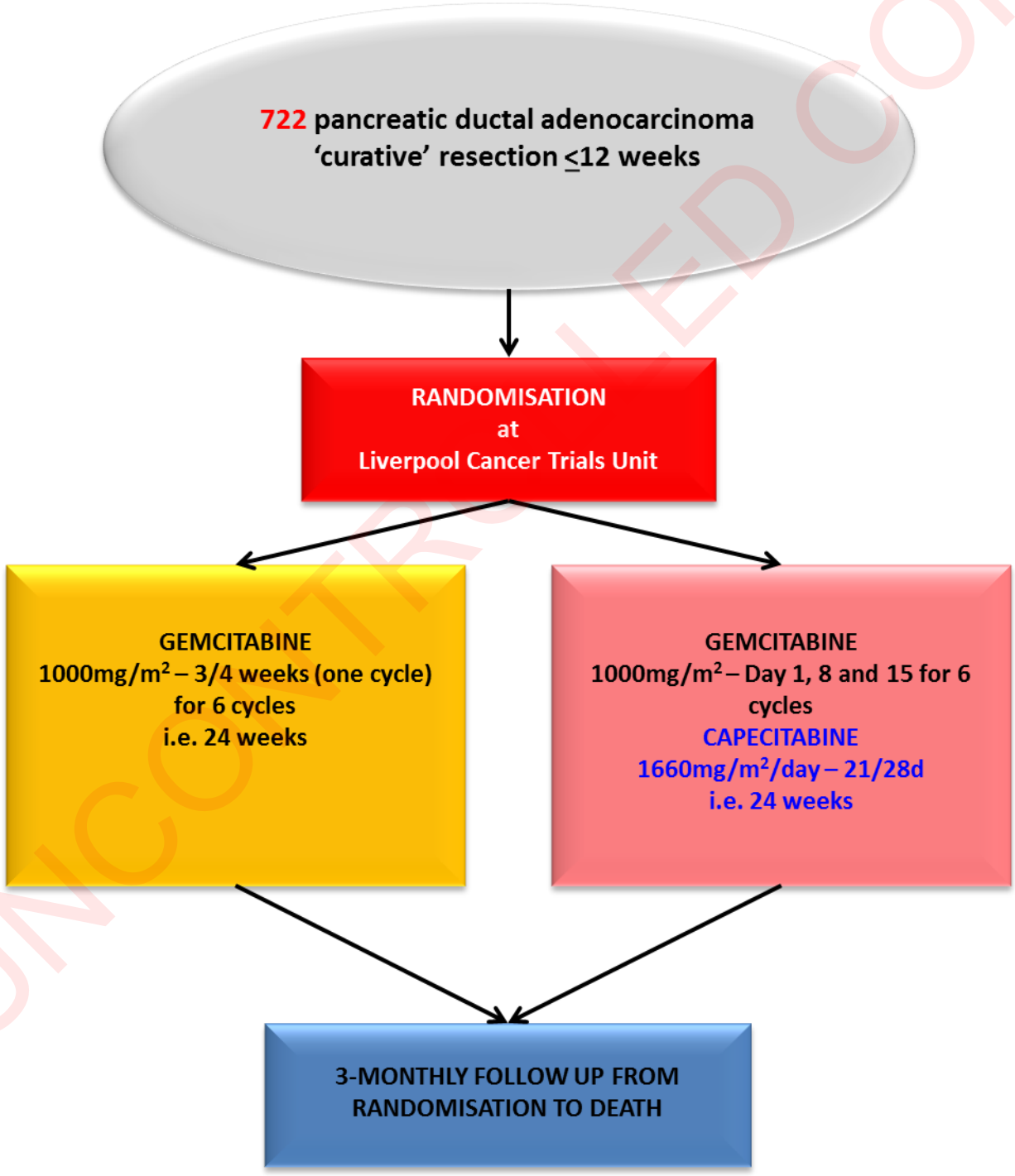
All statistical analyses will be carried out on an intention to treat basis, retaining patients in their randomised treatment groups and including protocol violators and

ineligible patients. A sensitivity analysis excluding any ineligible patients will also be conducted and reported.

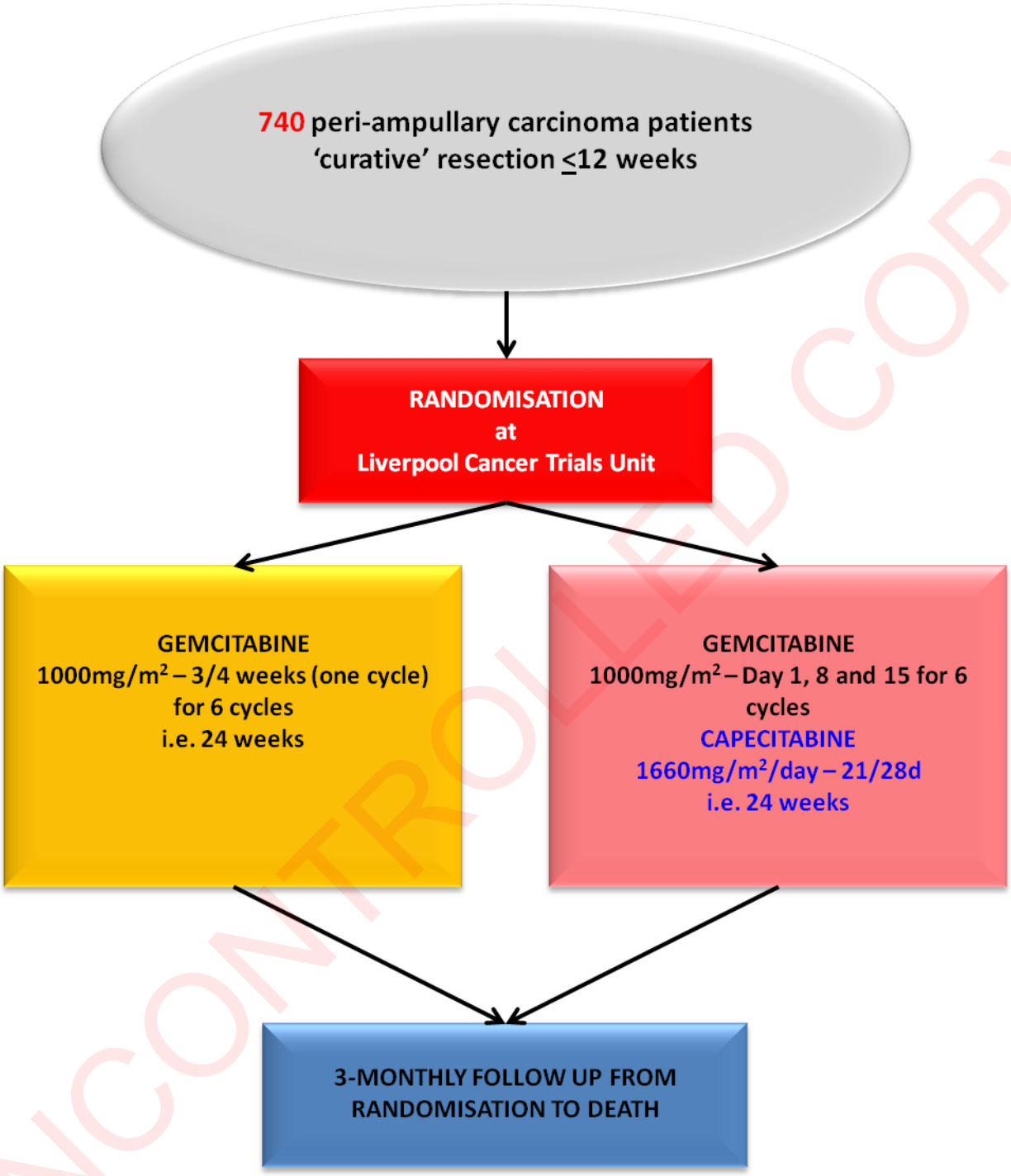
Survival analysis and final publication of these results will be carried out when all patients have a minimum of 2 years follow-up after randomisation. Survival data will also be analysed when all patients have been followed for at least 5 years to assess long-term treatment effects.

Four equally spaced interim analyses are planned after approximately 100, 200, 300 and 400 deaths. A futility analysis will also be carried out at each interim analysis.

Schematics of the Study Designs:



And:



N.B. UK sites will not recruit *Extrahepatic bile ducts - distal (ICD-O C24.0)* or *Small intestine (ICD-O C17)* tumour patients into the peri-ampullary cohort; these patients will be recruited only from non-UK centres.

5. Ethical and Regulatory Considerations

5.1. Independent Ethics Committees (IEC) and Regulatory Authority

Ethical review of the study is a legal requirement to safeguard the rights, dignity and welfare of people participating in research. The protocol and supporting documentation must be approved by/receive favourable opinion from the National Research Ethics Service (NRES) and the Medicines and Healthcare Products Regulatory Agency (MHRA) prior to patient recruitment. Amendments made to the study after a favourable ethical and regulatory opinion will be submitted and approved prior to implementation. The requirement for ethical and regulatory authority approvals applies to all participating countries.

The ESPAC-4 study received a favourable ethical opinion from Liverpool (Adult) Research Ethics Committee on the 04/03/08 and a Clinical Trial Authorisation from the MHRA on 20/02/08 to conduct the trial in the United Kingdom. The CTA reference is EudraCT: **2007-004299-38**.

Each participating Principal Investigator (PI) will be named on the original ethics and CTA applications form or on a subsequent substantial amendment. From April 2009 the responsibility for site specific assessment for NHS sites has been transferred from Local Research Ethics Committees (LRECs) to NHS R&D offices. Written evidence of NHS R&D approval must be made available to the CR-UK Liverpool Cancer Trials Unit prior to randomisation of subjects at site

Annual progress and safety reports and a final report at the conclusion of the trial will be submitted to the MREC and the MHRA within the timelines defined in the regulations.

5.2. Ethical Conduct of the Trial

The trial will be conducted to conform to: the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Seoul (2008) the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

This study may be terminated at the request of the Chief Investigator, Independent Data and Safety Monitoring Committee, Independent Ethics Committee or the regulatory authority (MHRA) if, during the course of the study, concerns about the safety of further dosing emerge.

The Chief Investigator will update the ethics committee and regulatory authority (MHRA) of any new information related to the study drug when appropriate.

5.3. Patient Information and Informed Consent

The consent process must be carried out by a medically qualified member of the research team. All patients will receive written and verbal information concerning the nature of the study, the known side effects that they might expect and the risks. This information will emphasise that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. All patients will be given opportunity to ask questions and will be given sufficient time to consider before consenting.
The patient's permission will also be sought pre- and post-surgery (where appropriate) to have samples of their plasma, urine and tissue stored for translational studies. The patients will be advised that they are free

to withdraw from the study without obligation at any time. The consent form will also request permission for their General Practitioner to be informed of their involvement in the study and also permission for personnel involved in the research or from regulatory authorities to have access to the subject's medical records.
Both the clinician taking consent and the patient must personally sign and date the form, in the presence of each other.

The original copy of the signed Consent Form will be retained by the Investigator in the Study File. A copy will also be filed in the subject's notes and a further copy of the signed Consent Form will be given to the subject. The completed consent form will be also faxed to the Liverpool Cancer Trial Unit with the randomisation paperwork. The patient's signed and dated informed consent to participate in the trial must be obtained prior to any trial related procedure and randomisation being carried out.

6. Study Administrative Structure

6.1. Chief Investigator

The Chief Investigator takes primary responsibility for the conduct of the trial and is responsible for approval of the protocol, CRF and the clinical report on behalf of all study investigators.

Professor John Neoptolemos
The Owen and Ellen Evans Chair of Cancer Studies
Head of School of Cancer Studies & Head Division of Surgery and Oncology
The Duncan Building
Daulby Street
Liverpool
L69 3GA

Tel: +44 (0) 151 706 4175
Fax: +44 (0) 151 706 5798
Email: J.P.Neoptolemos@Liverpool.ac.uk

6.2. ESPAC Working Group

The ESPAC Working Group is comprised of the Chief Investigator, other lead Investigators (clinical and non-clinical) and members of the LCTU. The ESPAC working group are responsible for the day-to-day management of the study.

Professor John Neoptolemos – Chief Investigator
Details as above

Mr Karl Harvey - Senior Trial Co-ordinator
Liverpool CR-UK Centre
Cancer Research UK Liverpool Cancer Trials Unit
1st Floor, C Block, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Tel: +44 (0) 151 794 8932 Fax: +44 (0) 151 794 8247
Email: Karl.Harvey@Liverpool.ac.uk

Prof. Fiona Campbell - Consultant Gastrointestinal Pathologist
Royal Liverpool University Hospital
Prescot Street
Liverpool
L7 8XP

Tel: +44 (0) 151 706 5887 Fax: +44 (0) 151 706 5859
Email: Fiona.Campbell@rlbuht.nhs.uk

Mr Richard Jackson – Trial Statistician
Liverpool CR-UK Centre
Cancer Research UK Liverpool Cancer Trials Unit
1st Floor, C Block, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Tel: +44 (0) 151 794 8834 Fax: +44 (0) 151 794 8247
Email: R.J.Jackson@Liverpool.ac.uk

Professor Markus Büchler - Chairman,
Department of Surgery
University of Heidelberg
Im Neuenheimer Feld 110
69120 Heidelberg
Germany

Tel: +49 (6221) 56 6201 Fax: +49 (6221) 56 5450
Email: markus_buechler@med.uni-heidelberg.de

Professor David Cunningham - Consultant Oncologist
Department of Medicine
Royal Marsden Hospital
Downs Road
Sutton
Surrey
SM2 5PT

Tel: +44 (0) 208 661 3156 Fax: +44 (0) 208 643 9414
Email: David.Cunningham@rmh.nhs.uk

Professor Paula Ghaneh - Consultant Surgeon
Liverpool CR-UK Centre
Cancer Research UK Liverpool Cancer Trials Unit
1st Floor, C Block, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Tel: +44 (0) 151 706 4062 Fax: +44 (0) 151 706 5826
Email: P.Ghaneh@Liverpool.ac.uk

Professor Dan Palmer - Consultant Oncologist
Division of Surgery and Oncology
The Duncan Building
Daulby Street
Liverpool,
L69 3GA

Tel: +44 (0) 151 706 4177 Fax: +44 (0) 151 706 5798
Email: Daniel.Palmer@Liverpool.ac.uk

6.3. Independent Safety and Data Monitoring Committee (ISDMC)

The Independent Safety and Data Monitoring Committee (ISDMC) will consist of the following independent members:

Mr Christopher Russell – Chair and Expert in pancreas surgery
Professor Daniel Hochhauser – Expert in oncology
Dr Roger Ahern – Statistician

The (ISDMC) will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene prior to the trial opening and will meet at approximately 6 monthly intervals. Their responsibilities will be defined in the ISDMC Charter and subsequent amendments which will be signed by all parties. The ISDMC will review the details of the planned interim analyses statistical analysis plan and will provide a recommendation to the Trial Steering Committee.

6.4. Trial Steering Committee

The Trial Steering Committee (TSC) will be responsible for the overall monitoring and supervision of the trial, reviewing data from other studies, resolving issues related to trial design, trial conduct and reporting and considering the recommendations of the ISDMC. The TSC provide advice through its Independent Chair and has the ultimate decision for the continuation of the trial.

The Trial Steering Committee will include but is not limited to the following:

- Independent Chairman (not involved directly with the trial)
- Independent Statistician
- Independent Advisor
- Independent Layman
- 1-2 Principal Investigators
- Chief Investigator
- Trial Co-ordinator ...etc

As with the ISDMC their responsibilities will be defined in the TSC Charter and subsequent amendments which will be signed by all parties.

6.5. Principal Investigator

Each participating Principal Investigator (PI) will be responsible for all aspects of trial conduct at their site. Each PI will be qualified by training and experience and should have adequate resources to properly conduct the trial. Prior to the study being initiated at site the PI must agreed to and sign an Investigator/Research Site Agreement to confirm their agreement to conduct the trial in compliance with GCP, the applicable regulatory requirements and the protocol.

6.6. Sub Investigators

Each participating sub-investigator will be responsible for aspects of trial conduct delegated to them by the Principal Investigator at their site as described in the delegation log, to be signed prior to those trial procedures being performed by the sub-investigator.

6.7. Co-Investigators

Participating co-investigators are researchers who will provide significant intellectual input into the research and will be responsible for the day to day running of some aspects of the trial conduct.

6.8. Sponsor

The study is co-sponsored by:

Representative of:

The Royal Liverpool and Broadgreen
University Hospitals NHS Trust
Prescot Street
Liverpool
L7 8XP

Representative of:

The University Of Liverpool
Research and Business Services
The Foresight Centre
3 Brownlow Street
Liverpool
L69 3GL

6.9. Trial Statistician

The Trial Statistician will input into the development of the protocol and provide advice on trial design, randomisation procedure, Case Report Form and database design. The trial statistician will plan and undertake all interim and final analyses of the trial data reporting results to the ISDMC and will prepare results for presentation and publications.

Mr Richard Jackson
Trial Statistician
Liverpool CR-UK Centre
Cancer Research UK Liverpool Cancer Trials Unit
1st Floor, C Block, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Tel: +44 (0) 151 794 8834
Fax: +44 (0) 151 794 8247
Email: R.J.Jackson@Liverpool.ac.uk

7. Introduction and Rationale: Pancreatic Ductal Adenocarcinoma

7.1. Introduction

Pancreatic cancer is one of the major causes of cancer death in Europe, the USA and globally with a five year survival rate of less than 5%[1-3]. The outlook for those patients who can undergo surgical resection is better. In specialised centres, resection rates of above 15% can be achieved[4]. Although surgery cannot guarantee a cure, the five year survival does improve to around 10% following resection[5,6] and increases to 20-30% with adjuvant chemotherapy[7]. There is a clear need to improve long term survival in these patients

7.2. Adjuvant chemoradiotherapy

There have been several randomised trials which have assessed adjuvant therapies in resected pancreatic cancer. Some of these showed promise but due to small numbers or the use of suboptimal regimens the results have not been emphatic[8-10]. The European Study Group for Pancreatic Cancer (ESPAC) 1 trial[11] was the first adequately powered, randomised study to assess chemoradiotherapy (split course (total 50Gy), concurrent with 5-fluorouracil(5-FU)) and chemotherapy (5FU, 425mg/m^2, d1-5 and folinic acid, 20mg/m^2, d1-5, repeated monthly for six months) in resected pancreatic cancer. Analysis of 550 patients with pancreatic ductal adenocarcinoma (median follow-up of 44 months) confirmed no survival benefit for chemoradiotherapy but showed an unequivocal significant survival benefit for chemotherapy. There was a survival benefit for adjuvant chemotherapy (5FU/FA) but not for adjuvant chemoradiotherapy (40Gy split course) in the final analysis of the 2x2 factorial group of 289 patients [7].

The failure of adjuvant chemoradiotherapy to improve survival observed in the ESPAC-1 trial was also reflected in the results of the EORTC multicentre prospective randomised trial by Klinkenbijl et al[12, 13]. Overall survival after follow-up of 11.7 years reaffirmed that there was no difference in overall survival between the two arms (death rate ratio 0.91, 95% confidence interval 0.68 to 1.23; p= 0.54). The overall 10 year survival was 18% in the entire population, and 8% in the subgroup of pancreas head cancers[13].

The results of these two studies appeared to contradict the original GITSG trial [14, 15] which used both chemoradiotherapy and follow-on chemotherapy in the treatment arm compared to surgery alone. Unfortunately this was a trial of only 43 patients, insufficient to provide convincing evidence for combination therapy against chemotherapy alone.

The Radiation Therapy Oncology Group Study 9704, a phase III trial [16], compared pre-and post-chemoradiation gemcitabine (at a dose of 1000mg/m^2/day) to pre- and post-chemoradiation 5FU (at a dose of 250mg/m^2/day given as a continuous infusion). Overall 538 patients were recruited but analysis was restricted to the 451 'eligible' patients, whereas in ESPAC-1 the analysis was a pure intention to treat. There was no difference in overall survival between the two arms (median survival 16.7 months for the 5-FU group versus 18.8 months for the gemcitabine group; p = 0.34).

A post hoc subgroup analysis of the 388 patients with pancreas head cancer revealed a median survival of 20.5 months and a 3-year survival of 31% in the gemcitabine group vs a median survival of 16.9 months and a 3-year survival of 22% in the fluorouracil group (hazard ratio, 0.82 [95% confidence interval, 0.65-1.03]; p = 0.09). The treatment effect was strengthened on multivariate analysis (hazard ratio, 0.80 [95% confidence interval, 0.63-1.00]; p = 0.05) [16]. The authors concluded that the addition of gemcitabine to adjuvant fluorouracil-based chemoradiation was associated with a survival benefit for patients with resected pancreatic cancer, although this improvement was not statistically significant [16].

Comparison with the individual groups in the ESPAC 1 trial suggests better survival times associated with 5-FU/FA alone (median survival 21.6 months) when compared with the combination group (and better survival overall). It is difficult to draw any meaningful conclusions from this trial apart from the fact that there

appeared to be no difference in survival whether 5-FU/FA or gemcitabine were used (pre- and post-chemoradiation).

The case for adjuvant chemoradiotherapy with follow on chemotherapy remains to be proven and does not provide a significant survival advantage over that seen with chemotherapy alone [17].

7.3. Adjuvant chemotherapy

The CONKO-001 trial [18] randomized 368 patients, of whom 179 were randomised to adjuvant gemcitabine and included in the primary analysis (intent-to-treat) and 175 randomised to surgery alone and included in the primary analysis and reported in 2007. The primary end point was disease free survival (DFS). The median (95% confidence interval) DFS for gemcitabine was 13.4 (11.4, 15.3) months and 6.9 (6.1-7.8) months for surgery alone ($p<0.001$, log-rank). The estimated DFS at 3 and 5 years was 23.5% and 16.5% respectively in the gemcitabine group and 7.5% and 5.5% respectively in the control group. Subgroup analyses showed (surprisingly) that the DFS effect of gemcitabine was significant in patients with either R0 or R1 resection. The estimated overall survival was 34% at 3 years and 22% at 5 years for the gemcitabine group and 20% at 3 years and 11% at 5 years for the surgery alone group. The median (95% CI) overall survival was 22.1 (18.4, 25.8) months in the gemcitabine group and 20.5 (17, 23.4) months in the control group (estimated overall hazard ratio was 0.79, with 95% CI = 0.62, 1.01; $p<0.06$, log-rank) [18].

By December 1st 2007 303 events (85.6%) have occurred for DFS and 293 events (82.8%) for overall survival [19]. Gemcitabine significantly improved the median overall survival [22.8 months] compared to the surgery alone group [20.2 months; p=.005] with estimated survival at 3 and 5 years of 36.5% and 21.0% respectively for the gemcitabine group vs. 19.5% and 9.0% respectively for the surgery alone [19].

The results from ESPAC-1 formed the basis of the ESPAC-3(v2) trial which was designed to identify if either adjuvant gemcitabine or 5-FU/FA was associated with significant better survival in patients with resected pancreatic cancer. The trial randomised 1030 patients with an R0/R1 resection for pancreatic ductal adenocarcinoma who received adjuvant therapy within 8 weeks of surgery. The final two year analysis was carried out on an intention to treat basis after 753 (69%) patients had died and was presented at ASCO 2009 [20]. Median survival from resection of patients treated with 5FU/FA was 23.0 (95% CI: 21.1, 25.0) months and for patients treated with gemcitabine this was 23.6 (95%CI: 21.4, 26.4) months. Log-rank analysis revealed no statistically significant difference in survival estimates between the treatment groups ($c^2_{LR}=0.7$; p=0.39; $HR_{GEM}=0.94$; 95%CI = 0.81, 1.08). There was no significant difference in the effect of treatment across subgroups according to R status (test of heterogeneity $c^2_1=0.3$, p=0.56).These results [20] provide the rationale for the use of gemcitabine as the control arm in ESPAC-4 trial.

7.4. Combination chemotherapy

There is now mounting evidence that combination therapy with gemcitabine is superior to gemcitabine alone in patients with advanced pancreatic cancer. The combinations of gemcitabine and erlotinib (epidermal growth factor receptor tyrosine kinase inhibitor) [21] or platinum based analogues or capecitabine [22-25] have proven to be superior to gemcitabine alone. The strongest evidence comes from the GemCap study [25] in which 533 patients, with advanced pancreatic cancer (71% with metastases), were randomised to either gemcitabine versus a combination of gemcitabine and capecitabine. The GEM-CAP regimen was shown to significantly improved objective response rate (19.1% v 12.4% respectively; p = 0.034) and progression-free survival ([HR = 0.78; 95% CI = 0.66, 0.93; p = 0.004) and was associated with a trend toward improved overall survival (HR= 0.86; 95% CI = 0.72, 1.02; p = 0.08) compared with gemcitabine alone [25].

A meta-analysis of two additional studies involving 935 patients showed a significant survival benefit in favour of GEM-CAP (HR = 0.86; 95% CI = 0.75, 0.98; p = 0.02) with no inter-trial heterogeneity [25].

7.5. Meta-analyses

ESPAC [26] performed a meta-analysis investigating the roles of adjuvant chemoradiation and chemotherapy following resection of pancreas ductal adenocarcinoma on survival. Five randomised trials which were included [8, 9, 11, 12, 14, 15] with individual patient data available in four (875 patients) out of the five selected randomised controlled trials (total number of patients with pancreatic adenocarcinoma=939). Assessment of adjuvant chemotherapy trials revealed a 25% significant reduction in the risk of death (HR = 0.75, CI = 0.64, 0.90; P_{strat}=0.001). The median survival was 19 months with chemotherapy and 13.5 months without. On the other hand, there was no significant difference in the risk of death with chemoradiation (HR = 1.09, 95% CI = 0.89, 1.32; P_{strat}= 0.43). Overall, the results of the meta-analysis are consistent with the conclusions of the ESPAC-1 study [7] that there is a significant benefit for patients with resected pancreatic cancer with adjuvant 5-FU/FA chemotherapy and indeed, patients who received chemoradiotherapy may even do worse than observation.

In order to determine the true benefit of adjuvant 5FU/FA versus surgery alone a meta-analysis of patients from ESPAC-1 and -3 and confirmed that 5FU/FA was active in the adjuvant context [27].

7.6. Summary of rationale for the Study

Long term survival following resection for pancreatic cancer still needs to be improved. Adjuvant 5-FU/FA demonstrates significant improvement in overall survival following surgery; adjuvant gemcitabine also demonstrates a survival advantage following surgical resection for pancreatic cancer. Gemcitabine plus capecitabine improves survival in patients with advanced pancreatic cancer compared with single agent gemcitabine.

Thus the ESPAC-4 trial aims to answer the question whether there is a survival difference between a single agent (gemcitabine) versus combination chemotherapy (gemcitabine plus capecitabine) in patients following resection for pancreatic cancer.

The study will randomise patients into one of two arms up to 12 weeks following pancreatic cancer resection surgery and treatment should aim to begin within 2 weeks of randomisation (or within 14 weeks or surgery). The two treatment arms will be gemcitabine plus capecitabine versus gemcitabine.

The primary outcome measure is overall survival. If one treatment shows superiority in terms of the primary and secondary endpoints, this could be recommended as a standard treatment in the UK.

7.7. Introduction and Rationale: Peri-ampullary Carcinoma

Peri-ampullary carcinoma, arising from the head of the pancreas in the region of the ampulla of Vater may be from one of at least five potential origins: pancreas, bile duct, the ampulla itself, the periampullary duodenum or other undetermined cell types [28,29]. The incidence rates are 11.7, 0.88, 0.49 and 0.01 per 10^5 for pancreatic, bile duct, ampullary and duodenal carcinomas respectively [30,31].

Although the incidence of non-pancreatic ductal periampullary adenocarcinomas is relatively low, collectively they represent approximately 40% of all resections for cancers in the head of the pancreas and represent a major cause of death.

It is important to distinguish the origin of the tumour as the clinical presentation is similar, but there is considerable variation in outcome [32,33]. The exact site of origin may be difficult to ascertain pre-operatively or prior to palliative therapy and may even be unclear in a significant proportion (~20%) in the final resection specimen [28,29]. Ampullary carcinoma can be classified into intestinal or pancreatobiliary type**s** the latter demonstrating a worse prognosis [34,35].

Until recently there were no studies to support treatment in the advanced or adjuvant setting. The EORTC 40891 trial randomized 92 patients with peri-ampullary tumours following resection to chemoradiation versus observation [13] and included 23 patients with bile duct cancer and two with duodenal cancers. There was no significant difference survival (RR = 0.91 [0.5-1.6], p= 0.737).

The ESPAC-3 trial randomised 1088 patients with resected pancreatic ductal adenocarcinoma to either adjuvant gemcitabine or 5FU/FA [36] and separately 434 patients with resected peri-ampullary tumours (310 ampullary, 89 bile duct, 9 duodenal, 26 other) to either surgery alone or adjuvant chemotherapy randomizing equally to 5FU/FA vs gemcitabine [37]. For the 367 (85%) with R0 resections chemotherapy provided increased survival (X^2 = 3.91; aHR= 0.73; p=0.048).

In the advanced setting the ABC-02 phase III trial randomised 410 patients with advanced biliary tract cancer to gemcitabine or gemcitabine plus cisplatin [38]. This included 20 patients with ampullary cancer and 73 with extrahepatic biliary cancer. The median overall survival was 11.7 months in the cisplatin-gemcitabine group and 8.1 months in the gemcitabine only group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001) [12].

As discussed above the results of adjuvant treatment for resected pancreatic cancer from ESPAC-3 and the results from the GemCap trial [25] form the justification for ESPAC-4.

As originally intended this rationale can now be extended to include patients with peri-ampullary cancers just as was undertaken in ESPAC-3, again with separate randomization and analyses.

There is considerable merit in including these patients as a major protocol amendment rather than a separate trial for the following reasons.

- The patients with peri-ampullary cancers present in a similar manner as pancreatic ductal cancer.
- The patients present to exactly the same teams and have exactly the same kind of surgery.
- The trial sites participating in Peri-ampullary ESPAC-4 will be largely the same as in Pancreatic Cancer ESPAC-4.
- This will save a huge amount of effort in terms of set-up and trial administration.
- Can be completed in the same time scale with the same resources – partly due to the scaling down in ESPAC-4 numbers from that originally planned.
- Model shown to work exceedingly well as demonstrated by ESPAC-3 [Periampullary] and ESPAC-3v2 [Pancreatic Ductal].

Ideally we would have wished to include periampullary cancer patients from the start but we lacked sufficient statistical knowledge of outcomes from the start of ESPAC-4 for pancreatic cancer patients.

Because this is an under-investigated area we lacked accurate survival data. We had to wait longer than anticipated to accrue sufficient events to enable accurate analysis of survival from Periampullary ESPAC-3. The wait has been worthwhile and has enabled us to come in now with a very powerful study design that has been readily accepted by the surgical and oncological communities.

N.B. UK sites will not recruit *Extrahepatic bile ducts - distal (ICD-O C24.0)* or *Small intestine (ICD-O C17)* tumour patients into the peri-ampullary cohort; these patients will be recruited only from non-UK centres.

8. Study Objectives

This randomised, multicentre phase III adjuvant study will test the following hypothesis:

Is there any survival difference between gemcitabine plus capecitabine versus gemcitabine alone when used as adjuvant therapy following resection (for both pancreatic ductal adenocarcinoma and peri-ampullary carcinoma patients)?

The outcome measures will be:

Primary Outcome: Pancreatic Ductal Adenocarcinoma: Length of survival.

Peri-Ampullary Carcinoma: Length of survival.

Secondary Outcomes: Pancreatic Ductal Adenocarcinoma:

1. Toxicity
2. Quality of life
3. Two year survival
4. Five year survival
5. Relapse free survival (RFS)

Peri-Ampullary Carcinoma:

1. Toxicity
2. Quality of life
3. Four year survival
4. Relapse free survival (RFS)

9. Investigational Plan and Study Population

9.1. Arm 1 – Gemcitabine alone

Gemcitabine 1000mg/m^2 is given as an i.v. infusion over 30-45 minutes (or local practice), the lyophilized powder being diluted in normal saline. This will be administered on day 1, 8 and 15 out of 28 days (one cycle) for six cycles i.e. 24 weeks. A 2 day window for the administration of gemcitabine is acceptable; this is to allow for public holidays or other miscellaneous reasons for a delay.

9.2. Arm 2 – Gemcitabine and Capecitabine Therapy

Gemcitabine 1000mg/m^2 is given as an i.v. infusion over 30-45 minutes (or local practice), the lyophilized powder being diluted in normal saline. This will be administered on day 1, 8 and 15 out of 28 days. A 2 day window for the administration of gemcitabine is acceptable; this is to allow for public holidays or other miscellaneous reasons for a delay.

Capecitabine 1660mg/m^2/day in two divided doses administered orally for 21 days followed by 7 days' rest (one cycle) for six cycles i.e. 24 weeks.

Patients will be advised that if a dose of capecitabine is missed, or vomited, they should carry on with the normal treatment schedule and not attempt to 'catch up' on doses.

9.3. Time Schedules

Date of enrolment of first patient:	10th November 2008
Planned date of enrolment of last patient:	2014 November
Planned date of last follow-up of last patient for final analysis:	2016 November
Planned date of last follow-up of last patient:	2019 November

9.4. Criteria for Patient Selection

9.4.1. Inclusion Criteria

1. A) Patients who have undergone complete macroscopic resection for ductal adenocarcinoma of the pancreas (R0 or R1 resection).
   Tumour types: pancreatic ductal adenocarcinoma or variants: adenosquamous carcinoma, mucinous non-cystic (colloid) carcinoma, signet-ring cell carcinoma, undifferentiated (anaplastic) carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, acinar cell carcinoma, acinar cell cystadenocarcinoma, intraductal papillary-mucinous carcinoma (invasive), mixed acinar-endocrine carcinoma, mixed ductal-endocrine carcinoma, mucinous cystadenocarcinoma, serous cystadenocarcinoma, solid-pseudopapillary carcinoma, miscellaneous carcinomas (specify).

   B) Patients who have undergone complete macroscopic resection for peri-ampullary carcinoma (R0 or R1 resection).
   Tumour types: peri-ampullary carcinoma: intestinal adenocarcinoma, pancreatobiliary adenocarcinoma, mixed intestinal/pancreatobiliary, indeterminate, other (specify).

   Permitted tumour locations: pancreas (ICD-O C25), ampulla of Vater (ICD-O C24.1), other (specify).
   Non-permitted tumour locations for UK sites only: extrahepatic bile ducts - distal (ICD-O C24.0), small intestine (ICD-O C17).

2. Completion of all pre-operative investigations.
3. Histological confirmation of the primary diagnosis.
4. Histological examination of all resection margins.
5. Patients randomised ideally within 12 weeks of surgery, although case by case the CI will consider patients up to 14 weeks, and can begin treatment ideally within 14 weeks of surgery.
6. No evidence of malignant ascites, liver metastasis, spread to other distant abdominal organs, peritoneal metastasis, spread to extra-abdominal organs – CT (chest, abdomen, pelvis) scan within 3 months prior to randomisation.
7. A WHO performance status $\leq$ 2
8. Creatinine clearance $\geq$ 50ml/min (according to Cockcroft and Gault or equivalent value following local practice)
9. Fully recovered from the operation and fit to take part in the trial.
10. Able to attend for administration of the adjuvant therapy.
11. Able to attend for long-term follow-up.
12. Life expectancy > 3 months.
13. No previous or concurrent malignancy diagnoses (except curatively-treated basal cell carcinoma of skin, carcinoma in situ of cervix).
14. No serious medical or psychological condition precluding adjuvant treatment.
15. Fully informed written consent given.

9.4.2. Exclusion Criteria

1. Use of neo-adjuvant chemotherapy or other concomitant chemotherapy.
2. Patients with pancreatic lymphoma.
3. Macroscopically remaining tumour (R2 resection).
4. Patients with TNM Stage IV disease.
5. Patients younger than 18 years.
6. Pregnancy.
7. New York Heart Association Classification Grade III or IV.
8. Previous chemotherapy.
9. All men or women of reproductive potential, unless using at least two contraceptive precautions, one of which must be a condom.
10. Patients with known malabsorption.
11. Patients with a baseline neutrophil count of $<1.5 \times 10^9$/l.
12. Patients with a baseline platelet count of $<100 \times 10^9$/l.
13. Patients with severe hepatic impairment.

9.5. Criteria for Withdrawal from Trial Treatment

Patients ***may*** withdraw from randomised treatment for any of the following reasons:
1. Patient decision to discontinue treatment.
2. Intolerable adverse effects as judged by an investigator or the patient.

Patients ***must*** withdraw from randomised treatment for any of the following reasons:
1. Pregnancy.
2. Recurrent grade 3 or 4 drug related toxicity despite dose modification.
3. Serious systemic allergic reaction to any of the study drugs e.g. angio-oedema, anaphylaxis.
4. Disease recurrence.

If a patient is withdrawn from randomised treatment this will be recorded on the End of Treatment Form in the CRF to capture date and reason(s) for treatment withdrawal. Withdrawing from treatment early does **not** mean the patient should be necessarily withdrawn from the trial altogether. Following withdrawal from

randomised treatment, patients will be treated according to local practice and will be asked to continue to be followed up in the study by 3 monthly hospital visits until death. Centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. If a patient does not wish to continue to be followed up in the study (section 7.4.6) a trial End of Study Case Report Form will be completed to capture date and reason for trial withdrawal.

9.6. Patient Transfer

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP. A copy of the patient's Case Report Forms (CRFs) should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. **The LCTU should be notified in writing of patient transfers.**

9.7. Withdrawal from Trial Completely

Patients who autonomously withdraw from the trial for reasons other than those listed above, have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. Such patients may need to reaffirm that they consent to follow-up through usual National Health Service (NHS) mechanisms. If the patient explicitly states their wish not to contribute further data to the study, the LCTU should be informed in writing by the responsible physician and an End of Study CRF should be completed.

10. Enrolment and Randomisation

10.1. Patient Screening and Enrolment

A log of all potential patients should be kept at each site, including individuals who decide not to participate in or who are found to be unsuitable for the study.

Screening will be performed upon a patient's possible eligibility for the study and must be documented on the "Screening and Enrolment log". If sites have agreed to take part in the pre-surgery sample collection, screening will begin when any potential subject is given the pre-surgery patient information sheet and consent form. At sites that are not involved in pre-surgery sample collection, screening is defined as beginning with the issuing of the ESPAC-4 Patient Information Sheet and Consent Form to the patient. All screening pre- and post-surgery is recorded on the same Screening and Enrolment Log. All patients will be issued a screening number and, where possible, for patients who are not randomised a reason is recorded.

10.2. Randomisation

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised by trained staff at the LCTU. To ensure essential entry criteria are fulfilled, randomisation can only occur following the completion and forwarding of the trial registration documents by the investigators:

- Registration and Pathology Proforma (including inclusion and exclusion criteria, country and resection margin status)
- Signed Consent Form
- Histopathology report

The randomisation documents should be faxed to the LCTU on Monday to Friday from 09:00 to 17:00 (UK time), fax number: 0151 794 8247. Prior to faxing documents, site staff should telephone 0151 794 8873/8932 to inform the LCTU staff of the incoming randomisation fax.

Personnel from the LCTU will review the randomisation documents, confirm eligibility and record essential demographic data. The patient will then be randomly allocated a trial treatment and given a unique trial number using a specially designed minimisation computer program. The randomisation form will be annotated with details of the treatment allocation, trial number and returned by fax to the investigator at site.

Randomisation and data storage will be controlled centrally by the Cancer Research UK Liverpool Cancer Trials Unit. Minimisation will be implemented for the allocation of treatments using a specially designed computer program, with the following stratification factors:

(i) Resection margin status (negative or positive) and
(ii) Country

Allocation to treatment arms is in a ratio 1:1. A random element will be incorporated in the minimisation algorithm to prevent the remote chance of predictability.

Randomisation – Tel: +44 (0) 151 794 8932, Fax: +44 (0) 151 794 8247

(N.B. The LCTU is open from 09:00-17:00 (UK time), Monday-Friday, excluding public holidays)

11. Investigational Medicinal Products

11.1. Investigational Product Description

11.1.1. Gemcitabine

Gemcitabine is a nucleoside analogue interfering with DNA replication.

Manufacturer	Generic gemcitabine sourced from manufacturers listed on the electronic Medicines Compendium or MHRA website are allowed for use in the study. http://emc.medicines.org.uk, www.mhra.gov.uk/
Formulation	Lyophilised power for solution for intravenous infusion
Packaging, Storage and Stability	Please refer to the specific SmPC for individual product
Supplier's Name	The local hospital pharmacy
Active Ingredient Name /Dose	Gemcitabine /2g, 1g and 200mg

Please refer to current Gemcitabine SmPCs supplied by the appropriate manufacturer, many of which can be found here:
http://emc.medicines.org.uk/searchresults.aspx?term=gemcitabine&searchtype=QuickSearch

11.1.2. Capecitabine

Capecitabine is a tumour selective fluoropyrimidine carbamate, which is converted to 5-fluorouracil. The final step is the conversion of 5' deoxy-5-fluorouridine to 5-fluorouracil by thymidine phosphorylase (TP), which is preferentially expressed in tumour tissues.

Manufacturer	Generic capecitabine sourced from manufacturers listed on the electronic Medicines Compendium or MHRA website are allowed for use in the study. http://emc.medicines.org.uk, www.mhra.gov.uk/
Formulation	Film-coated tablets for oral use
Packaging, Storage and Stability	Please refer to the specific SmPC for individual product
Supplier's Name	The local hospital pharmacy
Active Ingredient Name/Dose	Capecitabine / 150mg and 500mg

Please refer to current Capecitabine SmPCs supplied by the appropriate manufacturer, many of which an be found here:
http://emc.medicines.org.uk/searchresults.aspx?term=Capecitabine&searchtype=QuickSearch

11.2. Packaging and Labelling of Investigation Products

The packaging and labelling of the investigational products should be done in accordance with the Pharmacy Operating Manual.

11.3. Ordering of Investigational Products

The investigational products for ESPAC-4 will be provided from local supply chain (commercial stock) and NHS trusts will follow local procedures for ordering.

11.4. Preparation of Investigational Products

11.4.1. Preparation of Gemcitabine; Dose Calculations and Banding

Gemcitabine must be handled according to the instructions in the package insert. However if a pharmacy department has evidence that the gemcitabine can be stored for longer than the time specified in the appropriate SmPC, the drug can be reconstituted and stored according to local practice as long as the evidence for increased stability is documented in the Research Site Pharmacy File.

Dose banding:

- Calculate the patient's body surface area accurately to 2 decimal places, on the first day of each cycle, using the DuBois and DuBois formula (with height measured in centimetres):

$$BSA\ (m^2) = Weight\ (kg)^{0.425} \times Height(cm)^{0.725} \times 0.007184$$

- Calculate the **exact** (not rounded) target dose of gemcitabine.
- Use the table below to find the rounded dose category and the dose to be administered:

Table 1.

Dose Range (mg)	Dose to be administered (mg)
1050-1149	1100
1150-1249	1200
1250-1349	1300
1350-1449	1400
1450-1549	1500
1550-1649	1600
1650-1749	1700
1750-1849	1800
1850-1949	1900
1950-2049	2000
2050-2149	2100
2150-2249	2200
2250-2349	2300
2350-2449	2400
2450-2549	2500

- Where the above dose banding or BSA calculation **cannot** be followed exactly at a Research Site, local practise can be followed, this must be clearly documented in the Research Site Pharmacy File and a copy of the procedures sent to the co-ordinating centre (LCTU).
- Doses calculated and dispensed not according to the ESPAC-4 protocol dose banding set out above should be calculated to get the closest possible value and an accurate record of the dose given should be recorded on the appropriate on study CRF Page.

11.4.2. Preparation of Capecitabine; Dose Calculations and Banding

Capecitabine must be handled and stored according to the instructions in SmPC supplied by the appropriate manufacturer:

http://emc.medicines.org.uk/searchresults.aspx?term=gemcitabine&searchtype=QuickSearch

Dose banding:

- Calculate the patient's body surface area accurately to 2 decimal places.
- Use the table below to find the rounded dose category and the number of tablets per dose:

Table 2.

Body surface area (m^2)	Total daily dose (mg)	Number of tablets administered in the morning		Number of tablets administered in the evening	
		150mg	500mg	150mg	500mg
< 1.60	2500	0	2	0	3
1.60-1.80	2800	1	2	1	3
>1.80	3300	1	3	1	3

N.B. ***Capecitabine is only to be given for 21 days out of the 28 day cycle***

- Where the above dose banding or BSA calculation cannot be followed exactly at a Research Site, local practise can be followed, this must be clearly documented in the Research Site Pharmacy File and a copy of the procedures sent to the co-ordinating centre (LCTU).
- Doses calculated and dispensed not according to the ESPAC-4 protocol dose banding set out above should be calculated to get the closest possible value and an accurate record of the dose given should be recorded on the appropriate on study CRF Page.

11.5. Administration of Investigational Products

11.5.1. Gemcitabine Administration

1000mg/m^2 gemcitabine must be given as an intravenous infusion, the lyophilized powder being diluted in normal saline, over 30 minutes unless haematological toxicity occurs requiring dose adjustment as described below. Administer on day 1, 8 and 15 (one cycle) for six cycles i.e. 24 weeks. A 2-day window for the administration of gemcitabine is acceptable; this is to allow for public holidays or other miscellaneous reasons for a delay.

11.5.1.1. Haematological Toxicity – Dose adjustment

On the day of gemcitabine administration, the following dose should be given according to the absolute neutrophil and platelet counts on that day:

Table 3: Haematological Toxicity – Dose Adjustment

Absolute neutrophil count (x10^9/l)	Gemcitabine dose modification
> 1.0	100% of full dose
0.5 – 1.0	75% of full dose
<0.5	Omit for one week

Platelet count (x10^9/l)	Gemcitabine dose modification
> 100	100% of full dose
50 – 100	75% of full dose
<50	Omit for one week

Dose modification in subsequent courses following dose reductions

Patients who have had a dose reduction due to decreased neutrophil or platelet count should have their next dose according to neutrophil and/or platelet count on the day of gemcitabine administration, i.e. they can have their dose escalated back to 100% dose if their blood count is adequate. However, if after dose reduction to 75%, their blood count on the day of the next gemcitabine administration is still inadequate i.e. neutrophil count between 0.5-1.0 or platelet count between 50-100, the same dose (dose reduction to 75% of original dose) should be given. See table below.

Where dose omissions occur the dose should not be replaced and patients should maintain the same cycle schedule. Capecitabine should continue according to schedule where patients are allocated to gemcitabine + capecitabine.

Table 4: Haematological dose modification table.

Clinical Scenario	Gemcitabine dose for next treatment	Capecitabine dose for next treatment
Dose reduction for one week	Dose according to neutrophil and/or platelet count on that day	Continue 100%
Dose reduction for two consecutive weeks	75% of full dose with no re-escalation	Continue 100%
Initial dose omission for one week	75% of full dose with no re-escalation	Continue 100%
Recurrent dose omission or delay ≥ two weeks	75% of full dose with no re-escalation	75% of full dose with no re-escalation

If a patient has had a dose reduction with no plans for re escalation and experiences toxicity ≥ grade 2 the patient's dose would need to be further reduced by 25% (of the original dose).

11.5.1.2. Neutropenic Sepsis

Following an episode of febrile neutropenia, **all** subsequent courses should have the following dose adjustments:

Gemcitabine: Withhold until recovery then continue at 75% of the full dose with no re-escalation. If this occurs in a patient already receiving 75% of the full dose, then a further dose reduction to 50% of the full dose should be made.

Capecitabine: Withhold until recovery then continue at 75% of the full dose with no re-escalation. If this occurs in a patient already receiving 75% of the full dose, then a further dose reduction to 50% of the full dose should be made.

G-CSF may be used to treat neutropenic sepsis and/or as secondary prophylaxis with subsequent cycles, according to usual local practice.

11.5.1.3. Non-haematological toxicity

Modifications are not usually required. In exceptional cases, treatment delay may be necessary until the toxicity has resolved. If this happens, a 25% dose reduction should be made for all subsequent courses.

Gastrointestinal

Abnormalities of liver transaminase enzymes occur in about two thirds of patients, but they are usually mild, non-progressive and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired liver function. Nausea and vomiting are reported in one third of patients and are easily manageable with standard anti-emetics.

Allergy

A rash is seen in approximately 25% of patients and sometimes associated with pruritis. The rash is usually mild, not dose-limiting and responds to local therapy.

Oedema

Oedema occurs in approximately 30% of patients. Sometimes facial or pulmonary oedema may occur. It is usually mild to moderate, rarely dose-limiting and is usually reversible after stopping gemcitabine treatment.

Flu-like illness

20% of patients complain of fever, headache, back pain, chills, myalgia, asthenia and anorexia. Paracetamol may produce symptomatic relief.

Renal impairment

Mild proteinuria and haematuria are reported in 50% of patients, but are rarely clinically significant and are not usually associated with any change in serum creatinine. However, in very rare instances, cases of haemolytic uraemic syndrome have been reported. Hence, gemcitabine should be used with caution in patients with impaired renal function.

11.5.2. Capecitabine Administration

- Capecitabine tablets are available in 500mg and 150mg and should be administered morning and evening and swallowed with water.
- Administration of capecitabine should be within 30 minutes (before or after) a meal.
- If a patient vomits after taking a dose of capecitabine, the dose should **not** be taken again.
- Missed doses of capecitabine, whether due to toxicity or dosing error, should **not** be made up.
- If the total daily dose requires uneven distribution of tablets then the larger dose should be given in the evening.
- Dose banding should be followed for all patients and the total daily dose of 1660mg/m^2 must be administered unless toxicity occurs requiring dose adjustment as described below.

11.5.2.1. Dihydropyrimidine dehydrogenase deficiency

With any fluoropyrimidine regimen, the occasional patient is encountered (approximately 1-3%) whom has markedly exaggerated toxicity due to reduced 5FU catabolism. If this occurs, await full recovery and then re-start capecitabine at a 50% reduction.

11.5.2.2. Non-haematological toxicity – Dose Adjustment

The most frequent side effects reported are: diarrhoea, hand-foot skin reaction and stomatitis. The incidence of myelosuppression with capecitabine is extremely low.

With the onset of toxicities supportive care measures should be instigation as necessary; loperamide, pyridoxine and emollients, sulcrulfate etc.

The following dose modification of capecitabine refers to non haematological toxicities:

Table 5. Dose Modification for Capecitabine

Grading according to NCI-CTCAE v3.0	Occurrence	Action	Dose adjustment for next cycle (% of starting dose)
Grade 1		Supportive measures	100%
Grade 2	First appearance	Interrupt until resolved to grade 0-1	100%
	Second appearance	Interrupt until resolved to grade 0-1	75%
	Third appearance	Discontinue	N/A
Grade 3	First appearance	Interrupt until resolved to grade 0-1	75%
	Second appearance	Interrupt until resolved to grade 0-1	50%
	Third appearance	Discontinue	
Grade 4	First appearance	Discontinue permanently	Discontinue

Renal Impairment

During the study, creatinine clearance should be calculated. For patients with mild renal impairment (creatinine clearance 51-80ml/minute), no dose adjustment is necessary. For patients developing moderate renal impairment (creatinine clearance between 30-50ml/min) during treatment, a 25% dose reduction should be made to the dose of capecitabine. Patients who develop severe renal impairment (creatinine clearance <30ml/min) should be withdrawn from trial treatment.

Hepatic impairment

In the absence of safety and efficacy data in patients with hepatic impairment, Capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction. Administration of Capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment with Capecitabine may be resumed when bilirubin decreases to $\leq$ 3.0 x ULN or hepatic aminotransferases decrease to $\leq$ 2.5 x ULN.

11.5.2.3. Haematological toxicity

Haematological toxicity due to capecitabine is rare. Where haematological toxicity is encountered, the guidance in Table 5 (above) should be followed.

11.5.2.4. Neutropenic sepsis

As per section 11.5.1.2.

11.5.2.5. Capecitabine dose reduction tables

The corresponding number of tablets to be taken for each dose reduction level is given below.

For patients with a body surface area <1.60/m^2.

Table 6.

Dose level	Total daily dose (mg)	Number of tablets administered in the morning		Number of tablets administered in the evening	
		150mg	500mg	150mg	500mg
100%	2500	0	2	0	3
75%	1800	1	1	1	2
50%	1300	1	0	1	2

For patients with a body surface area between 1.60/m^2 and 1.80/m^2

Table 7.

Dose level	Total daily dose (mg)	Number of tablets administered in the morning		Number of tablets administered in the evening	
		150mg	500mg	150mg	500mg
100%	2800	1	2	1	3
75%	2150	0	2	1	2
50%	1450	1	1	2	1

For patients with a body surface area > 1.80/m^2

Table 8.

Dose level	Total daily dose (mg)	Number of tablets administered in the morning		Number of tablets administered in the evening	
		150mg	500mg	150mg	500mg
100%	3300	1	3	1	3
75%	2500	0	2	0	3
50%	1650	1	1	0	2

11.5.2.6. Management of chest pain whilst receiving capecitabine

- Fluoropyrimidines, including capecitabine, are known to rarely cause a syndrome of angina-like chest pain, thought to be due to coronary artery spasm.
- If patients develop angina-like pain whilst receiving capecitabine, then treatment should be discontinued immediately pending further clinical assessment.
- If the chest pain is deemed to be capecitabine related, then the patient should **not** recommence treatment with capecitabine.

11.5.2.7. Concomitant Medications

Medications to be used with caution:

- Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with anticoagulants such as warfarin. Patients taking warfarin concomitantly with capecitabine should be monitored regularly for alteration in their coagulation parameters (PT or INR). If possible, patients receiving capecitabine should be converted to low molecular weight heparin for the duration of their treatment.

- Patients receiving phenytoin concomitantly with capecitabine should be regularly monitored for increase phenytoin plasma concentrations and associated symptoms.

- There are no reports of interaction between capecitabine and metronidazole; however, caution is advised in its use for patients in combination therapy arm due to known interaction between 5- FU and metronidazole.

Medications to be avoided

- Dipyridamole and allopurinol use should be avoided

- Sorivudine (or sorivudine analogues e.g. brivudine) is contraindicated in patients receiving capecitabine.

- Other cytotoxic agents or investigational drugs are prohibited during this study.

11.5.3. Treatment Delays

Treatment delays should be avoided as far possible; the maximum allowable treatment omission is 3 weeks. Any patient whose treatment is omitted for longer than 3 weeks should discontinue therapy.
All patients who withdraw from treatment should remain on follow-up within the trial.

11.6. Over Dosage

11.6.1. Gemcitabine Over-dosing

There is no antidote for over dosage of gemcitabine. In the event of a suspected over dosage, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

11.6.2. Capecitabine Over-dosing

Manifestations of acute overdose include nausea, vomiting, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of over dosage should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

11.7. Drug Accountability and Compliance Checks

The Investigator is fully responsible for the Investigational Products at the site. Dispensing of medication may be delegated to, e.g. a hospital pharmacy as locally applicable.

The person responsible for dispensing the medication will be responsible for maintaining adequate control of the Investigational Products and for documenting all transactions with them (as a minimum batch number,

expiry date and dispense date must be documented). Investigational Products must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made.

Drug accountability logs must be completed for each patient and a coy sent to the LCTU with the 9 month follow-up paperwork.

11.8. Treatment Compliance

The majority of trial treatment will be administered during hospital outpatient visits, ensuring accurate monitoring of gemcitabine compliance.
In order to confirm compliance with capecitabine administration, patients will be given capecitabine blister sheets of tablets to be taken each morning and evening. Nursing staff will collect the used and unused sheets and record any circumstances of non-compliance on the CRF.

11.9. Prior and Concomitant Treatment

Concomitant treatment for conditions other than pancreatic ductal adenocarcinoma or peri-ampullary carcinoma may be continued throughout the trial without any change in dosage if allowed by the selection criteria. Use of concomitant treatment (should include complementary, herbal and homoeopathic medicines plus supplement products) must be recorded in the patient's medical record and the CRF (drug name, dose, indication and dates of start and stop).

Use of non-marketed/other investigational products during the trial is not permitted.

Use of drugs for the treatment of the indication being studied is not permitted.

If vomiting, patients should be treated with anti-emetics, as per local policy.

11.10. Medicines to be used with caution/to be avoided

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with anticoagulants such as warfarin and phenprocoumon. The mechanism of interaction is unclear. These events occur within several days and up to several months after initiating capecitabine therapy and, in a few cases after stopping capecitabine. Patients taking warfarin concomitantly with capecitabine should be monitored regularly for alteration in their coagulation parameters, Prothrombin Time (PT) or International Normalized Ratio (INR)).

Dipyridamol and allopurinol use should be avoided and concomitant administration of capecitabine and sorivudine (or sorivudine analogues, e.g. brivudine) is contraindicated. Patients receiving phenytoin concomitantly with capecitabine should be regularly monitored for increase phenytoin plasma concentrations and associated symptoms.

There are no reports of interaction between capecitabine and metronidazole; however, caution is advised in its use for patients in combination therapy arm due to known interaction between 5-fluorouracil and metronidazole.

All medication necessary for the well being of the patient, and which is not expected to interfere with the evaluation of study drug, may be given at the discretion of the investigator. Particular attention should be paid to treatment that could influence the intended effects or mask side effects of treatment.

Patients who develop life-threatening signs or symptoms may be treated with corticosteroids. These patients however, may not be evaluable for immunological responses.

12. Study Procedures and Assessments

Table 9. Arm 1 – Gemcitabine alone – Schedule of Study Procedures

Study phase	Baseline		Rand	Treatment Phase (starting ideally within 14 weeks of surgery). One full cycle shown, repeated five times for a total of six cycles.																										End of Trt	3 Monthly Follow-up	End of Study
Day	Op[β]	≤14	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	-	3 – 60m	-
Histology/Cytology	X																																	
Informed Consent		X																																
Demography & Medical History		X																																
ECG		X																																
CT Scan	X[Δ]			To be performed at any point (as deemed necessary by the PI) to confirm clinical suspicion of disease progression																														
Enzyme Supplements		X		LCTU to be informed *if* the patient is taking enzyme supplements; they are not compulsory.																												X	
CRP		X																														X	
CA19-9		X																														X	
Inclusion Criteria		X																																
Randomisation			X																															
Physical Examination		X																													X	X		
Vital Signs		X																													X	X		
WHO Performance Status		X		X																											X	X		
Serum Chemistry		X*																														X		
Full Blood Count		X*		X[=]							X[=]							X[=]							X[$]							X		
Quality of Life Study		X*																														3, 6, 12, 18, 24, 36, 48, 60		
Translational Study Blood Sample [£]	X	X Taken prior to start of chemo																														3m only		
Translational Study Urine Sample [£]	X	X Taken prior to start of chemo																														3m only		
Concomitant Therapy		X		Monitored & recorded throughout treatment																												X	X	
Adverse Events				Monitored continuously and recorded as they occur, reported at 9 months. SAEs reported to LCTU within 24 hours.																												X	X	X
Gemcitabine Treatment				X[+]							X[+]							X[+]																
Capecitabine Treatment																																		
Reason for Discontinuation																																X		X
Death Form Completed				To be completed at any time death occurs																														

[β] Op time point is not specific but is related to activity at or close to the date of operation. [Δ] To be done within 3 months prior to randomisation. [£] Optional study. * Assessments should be made prior to randomisation but after consent given. [$] 1st cycle **only**. Adverse events are assessed according to NCI CTCAE version 3. Serious adverse events are reported to LCTU within 24 hours of site being notified.
[+] A 2 day window for gemcitabine administration is acceptable. [=] If it is local practice, FBC may be taken up to 2 days prior so that the results are ready on days 1, 8 and 15 of each cycle.

Table 10. Arm 2 – Gemcitabine & Capecitabine – Schedule of Study Procedures

Study phase	Baseline		Rand	Treatment Phase (starting ideally within 14 weeks of surgery). One full cycle shown, repeated five times for a total of six cycles.																										End of Trt	3 Monthly Follow-up	End of Study
Day	Op[β]	≤14	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	-	3 – 60m	-
Histology/Cytology	X[#]																																	
Informed Consent		X																																
Demography & Medical History		X																																
ECG		X																																
CT Scan	X[Δ]			To be performed at any point (as deemed necessary by the PI) to confirm clinical suspicion of disease progression																														
Enzyme Supplements		X		LCTU to be informed *if* the patient is taking enzyme supplements; they are not compulsory.																												X	
CRP		X																														X	
CA19-9		X																														X	
Inclusion Criteria		X																																
Randomisation			X																															
Physical Examination		X																														X	X	
Vital Signs		X																														X	X	
WHO Performance Status		X		X																												X	X	
Serum Chemistry		X*																															X	
Full Blood Count		X*		X[=]							X[=]							X[=]						X[$]									X	
Quality of Life Study		X*																															3, 6, 12, 18, 24, 36, 48, 60	
Translational Study Blood Sample [£]	X	X Taken prior to start of chemo																															3m only	
Translational Study Urine Sample [£]	X	X Taken prior to start of chemo																															3m only	
Concomitant Therapy		X		Monitored & recorded throughout treatment																												X	X	
Adverse events				Monitored continuously and recorded as they occur, reported at 9 months. SAEs reported to LCTU within 24 hours.																												X	X	X
Gemcitabine Treatment				X[+]							X[+]							X[+]																
Capecitabine Treatment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Reason for Discontinuation																																X		X
Death Form Completed				To be completed at any time death occurs																														

[β] Op time point is not specific but is related to activity at or close to the date of operation. [Δ] To be done within 3 months prior to randomisation. [£] Optional study. * Assessments should be made prior to randomisation but after consent given. [$] 1st cycle **only**. Adverse events are assessed according to NCI CTCAE version 3. Serious adverse events are reported to LCTU within 24 hours of site being notified.
[+] A 2 day window for gemcitabine administration is acceptable. [=] If it is local practice, FBC may be taken up to 2 days prior so that the results are ready on days 1, 8 and 15 of each cycle.

12.1. Follow-up and Quality of Life

- Patients will be followed up 3-monthly **from randomisation** for a minimum of 5 years but ideally until death.
- Follow-up Case Report Forms will be completed on each visit and should be submitted to the LCTU monthly.
- Quality of life forms (EORTC QLQ C-30) and WHO performance status will be completed at randomisation, at 3, 6, 12, 18 and 24 months, and annually thereafter up to 5 years.

12.2. Vital Signs

Vital signs will consist of blood pressure, temperature, respiratory rate, pulse rate.

12.3. WHO Performance Status

Performance Status must be assessed according to the WHO Performance Status (Appendix 2).

12.4. Electrocardiogram (ECG)

An electrocardiogram must be obtained from the patient prior to randomisation to ensure the patient is not suffering from any cardiac conditions which would preclude treatment with any of the investigational drugs.

12.5. CT Scan and Relapse Free Survival (RFS)

CT scans of the chest, abdomen and pelvis must be performed within 3 months prior to randomisation.

RFS will be recorded during the trial using clinical and biochemical diagnosis (CA19-9). If present, a CT scan should be performed to confirm clinical suspicions in accordance with standard clinical practice.

12.6. Concomitant Therapy

Use of prior and concomitant medications and therapies (e.g. radiotherapy, surgical procedures) should be recorded throughout treatment.

12.7. Reason for discontinuation

The reason for discontinuation of study treatment should be clearly documented and the End of Treatment form.

The reason for discontinuation on the study altogether should be recorded on the End of Study Form.

If a patient randomised to arm 2, GemCap, permanently discontinues taking capecitabine but carries on taking gemcitabine they are considered to be off trial treatment from that point. An end of treatment CRF should be completed and the off-trial gemcitabine therapy should be captured on a concomitant medications CRF.

If a patient ends trial treatment early they are expected to continue with follow-up (and quality of life) as ending trial treatment early does not mean they should necessarily be withdrawn from the study as a whole.

12.8. Laboratory Assessments – Local Analysis

All routine blood samples will be analysed locally according to local practice. Reference values from each laboratory must be provided to CR-UK Liverpool Cancer Trials Unit and amended if changed during the study period.
The following analysis should be performed at screening:

- CA19-9
- CRP
- Bilirubin
- Haemoglobin
- WBC
- Neutrophils
- Lymphocytes
- Platelets

These tests are repeated at each 3-monthly follow-up visit with the exception of bilirubin.

During the treatment phase a full blood count (haemoglobin, WBC, neutrophils, lymphocytes and platelets) is performed before each cycle of chemotherapy to assess toxicity.

This should be recorded on the **previous** cycle CRF treatment form. i.e. bloods taken prior to chemotherapy administration on day 8 of a cycle should be recorded on the day 1 CRF as the toxicity **after** the first week of treatment.

Bloods should also be taken within 7 days of the end of the last cycle and recorded on the last treatment CRF (Cycle 6 Week 3).

All other assessments should be carried out according to local practice and at the discretion of the PI.

12.9. Translational samples

The translational element of the trial will involve the collection and storage of frozen tissue, formalin fixed paraffin embedded tissue, blood cell, serum and plasma samples. The aim of the study is to identify an expression profile in tumours associated with good or poor response to capecitabine or gemcitabine, allowing correlation with somatic and germline genetic features facilitating development of a practical molecular response signature. Analysis of key enzymes and nucleoside transporters involved in gemcitabine and capecitabine metabolism and uptake (including polymorphisms) will be performed.

It has been recognised that some Research Centres participating in the ESPAC-4 trial will not have the facilities, staff or organisational structure that will allow the taking of sample from patients. Each site is encouraged to participate and efforts will be made to make the process as easy and accessible as possible.

The following samples to be collected prior to surgery, prior to adjuvant chemotherapy and at the 3 month follow-up visit:

- Urine samples – taken after fasting on the morning before surgery; 50ml of mid flow urine being stored immediately after sampling at -80 degrees Celsius; also prior to surgery

- Blood sample – 9ml will be taken in KE/9ml tube (Sarstedt Monovette) for plasma and cells and a 7.5ml blood sample will be taken in a Z/ 7.5ml tube (Sarstedt Monovette) for serum. Plasma will be separated from cells following approved protocols and the cells plasma and serum will be stored at -80 degrees Celsius.

The following samples to be collected during surgery:

- Tissue samples – trucut biopsies will be frozen in liquid nitrogen in theatre following approved SOPs; subsequent to pathological analysis, sections will be frozen in local pathology departments (again following approved SOPs) and paraffin embedded blocks prepared and sections H&E stained for preliminary characterisation of the blocks.
- Pancreatic juice (optional) – this will be aspirated from the pancreas during surgery, spun down and frozen at -80°C following approved SOPs and/or local practice.

Patients will be retrospectively classified according to survival after surgery. RNA extracted from tumours will be used to challenge arrays. Gene expression and sample classification profiles will be examined.

12.9.1. Collection and Storage of Tissue

1. Each centre will have subtle variations in procedure for fixation of tissues and procedures for taking and storing samples for freezing. All centres however, should aim to process samples within 30 minutes of removal from the patient. For the purposes of analysis the ESPAC-4 sample database will contain a field identifying the centre where the sample was taken by a code number. The Division of Surgery and Oncology (DSO) standard operating procedure (SOP) for freezing of samples is based on the SOP of the Department of Pathology in Verona and will be made available to other centres for subsequent storage of samples. The SOP will be attached to the Site Operating Manual but in brief involves the use of a sterile pair of forceps to place the right amount of tissue (too large a quantity will not pass through the neck of the tube when frozen) into Nunc tubes containing 1ml of isopentane. The lid of the Nunc tube is then closed and it is dipped gently into a liquid nitrogen container.
2. The Liverpool Department of Pathology SOP for fixation and processing of paraffin embedded tissues is similar to that used by the other centres. This takes account of the penetration time of 10% phosphate buffered formalin i.e. 2mm/hour as well as at least a 10:1 ratio of fixative to tissue. For the small size of the samples routinely collected, overnight fixation is recommended followed by processing on the VIP Processor and subsequent paraffin embedding. Again variation in fixation from different centres will be recoded on the database.

12.9.2. Collection and Storage of Blood

The DSO and ESPAC-4 team will circulate SOPs for the processing and storage of plasma, serum and urine. The content of these SOPs will be determined by the facilities available at the research site. Sampling kits containing all the required equipment to follow the SOP will be sent out as required. Where possible we will request that samples are spun down at site and stored at site at -80°C.

12.9.3. Collection and Storage of Urine

Urine samples will also be collected at the specified time points throughout the study. These samples will be stored in appropriate conditions within the Division of Surgery and Oncology, University of Liverpool, for at least 15 years from study start and will be used in future proteomic analysis e.g. analysis of tumour markers. The patient will be asked to collect mid-stream urine (approximately 50ml). Within 15 minutes of collection the urine samples should be placed on ice. The urine will be placed at -80°C as rapidly as possible and stored on site. Urine will only be collected in centres with facilities to store at this temperature. These centres will ship the samples to the Liverpool Experimental Cancer Medicine Unit on dry ice in batches.

12.9.4. Optional Collection and Storage of Pancreatic Juice

Optionally, if sites have the facilities and/or resources to do so, a sample of pancreatic juice may be aspirated during surgery. 1ml of phosphate buffered saline may be required for this procedure. The sample should be spun down and frozen at -80^{o}C.

13. Safety Reporting

13.1. Definitions

13.1.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs include the following:

- All suspected adverse medication reactions,
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. *Note that if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as two separate AEs.*
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. *Laboratory abnormalities associated with a clinical event (e.g. elevated liver enzymes in a patient with jaundice) should be described in the comments of the report of the clinical event rather than listed as a separate AE.*

13.1.2. Serious Adverse Event (SAE)

Severity of any AE will be graded according to the World Health Organisation (WHO) toxicity criteria/National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3, where applicable.

For each episode, the highest severity grade attained should be reported.

If an AE occurs that is not listed in the WHO/CTCAE, the Investigator will evaluate its severity using the definitions in Table 11.

Table 11: Definition of Severity of Adverse Events

Mild	Grade 1: Does not interfere with subject's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2: Interferes to some extent with subject's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3: Interferes significantly with subject's usual function (incapacity to work or to do usual activities [unacceptable])
Life Threatening	Grade 4: Results in risk of death, organ damage, or permanent disability (unacceptable)
Death	Grade 5: Results in death (unacceptable)

Note the distinction between the seriousness and the intensity of an AE. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed below:

- results in death or is life-threatening*
- requires hospitalisation or prolongation of hospitalisation
- results in persistent or significant disability or incapacity
- results in congenital anomaly

* The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.

Serious adverse events will be followed-up until progressive disease or death.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

13.1.3. Serious Adverse Reaction (SAR)

An SAE as defined above that is considered related to any dose of the Investigational Medicinal Product (IMP) administered to that participant.

13.1.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any suspected adverse reactions related to an IMP that is both unexpected and serious.

13.2. Assessment of Adverse Events

13.2.1. Severity

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant and the CI.

13.2.2. Causality (relationship to study drug)

The assignment of the causality should be made by the Investigator responsible for the care of the participant and the Chief Investigator (CI) using the definitions below. If any doubt about the causality exists the local Investigator should inform the LCTU who will notify the CI.

None: there is no evidence of any causal relationship. An alternative cause should be given.

Unlikely: there is little evidence to suggest a causal relationship (e.g. the events did not occur within a reasonable time after administration of the trial medication. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).

Possibly: there is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of trial medication. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probably: there is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Highly Probable: there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

This assessment is to be undertaken by the clinician responsible for the patient.

Highly Probable, probably or possibly related = adverse reaction
Unlikely or not related = other adverse event.

13.2.3. Expectedness

The ESPAC-4 CI or delegated other will evaluate each SAE as to whether it is expected or not. The event is considered as "unexpected" if it adds significant information on the specificity or severity of an expected event. The expectedness of an SAE/SAR should be determined according to the criteria in the appropriate summary of product characteristics (SmPC) reference document.

13.3. Reporting

13.3.1. Adverse Events

Adverse events that occur within 28 days following the last dose of trial treatment will be recorded in the case report form and are not part of the expedited reporting procedure.

The site staff should fill in one AE form per type of event, e.g. all episodes of vomiting should be recorded on one form and all episodes of neutropenia should be recorded on a separate AE form. This is so that changes regarding each event can be followed easily when inputting the data.

Completed AE forms will be requested from all research sites as part of the 9 month follow-up Case Report Forms (CRF) collection or upon death

13.3.2. Serious Adverse Event Reporting

Investigators **MUST REPORT ALL SERIOUS ADVERSE EVENTS (SAEs),** including disease related as well as treatment related events that occur between the start of trial treatment up to 28 days following the last dose of trial treatment.

SAEs occurring in patients who have NOT received any study treatment do not need to reported to the sponsor (e.g. patients consented but not yet randomised).

SAEs must be reported within **24 hours** of sites becoming aware of them by faxing a completed **SERIOUS ADVERSE EVENT FORM** (Appendix 11) to the Liverpool Cancer Trials Unit, Fax: +44 (0) 151 794 8247/8930/8931. The person reporting the event should also phone the Trial Co-ordinator on Tel: +44 (0) 151 794 8932/8873/8161 to alert that an SAE is being reported. On reporting an SAE to the LCTU, research sites will receive an acknowledgement. This will either be in as an email or a fax. If a receipt has not been received within two hours of submitting the SAE please ring the ESPAC-4 trial team on +44 (0) 151 794 8932.

If the electronic reporting system is not available and/or Case Report Forms are not available from the LCTU website, research sites should ring the LCTU on +44 (0) 151 794 8932/8873/8161 and report the SAE verbally and then complete the generic SAE form supplied prior to research site activation.

The Investigator must initiate appropriate therapeutic action and follow-up measures in accordance with Good Medical Practice but should notify the Trial Co-ordinator of such actions.

The minimum dataset required for a preliminary report should include the following.

Page 1

- Research subject trial number and initials.
- Treatment arm
- Date of onset of event
- Brief description of event and CTC or severity grade
- Outcome
- Dated signature of investigator/co-investigator and clearly printed name

Page 2

- Definition of serious
- Causality relationship
- Dated signature of investigator/co-investigator and clearly printed name

Page 3

- Date of last administration of study drug(s).
- Dated signature of investigator/co-investigator and clearly printed name.

13.3.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

The LCTU is undertaking duties delegated by the trial co-sponsors, Royal Liverpool & Broadgreen University Hospital NHS Trust and the University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and main REC) and co-sponsors as follows:

The minimum data required for initial reporting is:

- The suspected Investigational Medicinal Product (IMP)
- An identifiable subject
- An adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
- An identifiable reporting source

The Chief Investigator and the Liverpool Cancer Trials Unit will ensure that all SUSARs are reported to Competent Authorities and Ethical Committees.

- Fatal or life threatening SUSARs < 7 days* after receiving the information.
- All other SUSARs <15* days after receiving the information

*The start of these timelines is when the fax report arrives in the LCTU.

The Chief Investigator and the Liverpool Cancer Trials Unit will **inform all investigators of SUSARs**. Depending on the nature of the event determined by the CI this will be done as an event occurs or in a quarterly line listing.

13.3.4. Annual Reporting to MHRA and MREC

From September 2011 the sponsor will submit a Development Safety Update Report (DSUR).

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product; it will cover the following four areas:

(1) Examine whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety

(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects

(3) Summarise the current understanding and management of identified and potential risks

(4) Provide an update on the status of the clinical investigation/development programme and study results.

Annual safety reports will cover the period up to 28 days after the last patient has had the last dose of trial treatment. Therefore, annual safety reports will not need to be submitted subsequent to that period being covered as there will be no additional information.

13.3.5. Reference Safety Information

The reference safety information for **gemcitabine** is section 4.8 of the Gemzar (Eli Lilly) SPC. The reference safety information for **capecitabine** is section 4.8 of the Xeloda (Roche) SPC. The current versions of each SPC, applicable to the trial and current reporting period, are available on the LCTU portal (www.LCTU.org.uk).

14. Quality Assurance/Audit

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The ESPAC-4 trial investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent authorities (national or foreign) or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsor's site(s), CR-UK Liverpool Cancer Trials Unit or at any investigator's site including laboratories, pharmacies, etc.).

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTU communication strategy for multicentre trials. This includes management systems for the Green light process prior to drug release to site, conforming to the total Quality Management System currently operating within the LCTU.

14.1. Quality control for surgery

Signed CVs of all clinicians and research staff will be submitted to the LCTU prior to the site opening to recruitment for the ESPAC-4 trial. This is in line with established LCTU systems and processes for ensuring the highest standard of governance for clinical trials. Appendix 9 of the protocol provides definitions and guidelines to the extent of resection. These must be adhered to and signed up to by all investigators participating in the trial. Any complications which arise during surgery must be recorded on the patients' CRFs.

The Trial Co-ordinator maintains a communication strategy with all centres and will sign post any centre requiring clarification in the procedure. As part of the ESPAC group, investigators attend regular Steering Committee meetings which include continuous review and discussion including the definition of resectability. Advice is available to all investigators from experts in the field at any point during the trial. Further evidence will be available from pathological review.

14.2. Pathology quality control and guidance for pathology assessment of resection specimens

Appendix 8 of the protocol provides reference for the UICC, 7th Edition (2009) classification of malignant tumours. As part of the QC process, there will be a full pathology review of 10% of patients. These will be centrally reviewed in designated sites within the UK.

Dissection:
The method of dissection of the resection specimen will depend upon the individual specimen and the individual pathologist's preferred dissection technique (e.g. opening the main pancreatic duct/common bile duct or not, axial or bivalve slicing of the specimen).

Whichever approach is used, it is important that the specimen is sampled thoroughly to enable completion of all the boxes on the 'Pathology Proforma – Histological Information' which should be submitted with the 'Patient registration and randomisation form'. The following notes refer to specific requirements for the pathology proforma.

Macroscopic description:

- The maximum tumour dimension should be measured. This can be amended following histological examination.
- Named vessels should also be identified and recorded.

Block taking:

- It is important that a 'block code' is kept, clearly indicating the site of origin of each block (e.g. 'tumour posterior margin', 'anterior pancreatoduodenal lymph node(s) above ampulla – 17a'). This will aid the pathology review process.
- It is imperative that all resection margins are examined histologically (see 'Inclusion criteria'), as well as all named vessels and all lymph nodes.
- The number of tumour blocks taken will depend upon the individual specimen but should be sufficient to allow assessment of tumour size, histological type, grade/differentiation, perineural invasion, and resection margin status.

Microscopic description:

- For the purposes of this trial, a positive resection margin is defined as tumour at, or within 1mm of, ANY margin (including the anterior surface). This resection margin involvement may be either by direct tumour invasion and/or by lymph node involvement, and should be recorded in the separate boxes on the pathology proforma.

Staging:

- The 7th (2009) edition of the UICC TNM classification of malignant tumours is to be used for staging.

Pathology review:

- All of the histology slides from 10% of the cases (randomly selected) will be reviewed centrally as part of ongoing audit and quality assurance.

14.3. Risk assessment

In accordance with the LCTU Standard Operating Procedure a risk assessment will be completed in partnership with:

- Representatives
- Trial Sponsors
- Trial Co-ordinator
- LCTU Manager
- Trial Statistician

In conducting this risk assessment, the contributors consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:

Score ≤ 33% = Low risk
Score ≥ 34 to ≤67% = Moderate risk
Score ≥ 68 to ≤ 100% High Risk

The LCTU will review recruitment rates, withdrawals and losses to follow-up and identified problems will be reviewed by the TMG and remedial action taken as necessary. Data submitted to the database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the trial protocol. Data will be checked for unusual values (range checks) and checked for consistency with participants over time. Discrepancies that have been raised can be queried, and resolved at the LCTU, or by contact with the individual site. A complete log of discrepancies and data amendments including the data amendments including the date of each change, and the person who changed it will be kept.

15. Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Paper case report forms will be labelled with patient initials and their unique ESPAC-4 trial randomisation number (or screening number, if appropriate). Laboratory results and consent forms sent to the Liverpool Cancer Trials Unit as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Any identifiable information will be stored separately from the patients' CRF folders in secure, locked cabinets.

16. Case Report Forms and Data Handling

16.1. CRFs

The CR-UK Liverpool Cancer Trials Unit will provide the investigators with Case Report Forms (CRFs) via the unit website (http://www.LCTU.org.uk/). CRFs are uploaded onto the webpage by authorised members of LCTU staff and the system has been fully validated prior to going live.

Each Investigator and/or designated personnel will be issued with a username and password and instructions for the web-based CRF system after the 'Green Light' for that site has been given. Investigators will be instructed to download and print off forms as and when they are required and not to save them to their local computer. This ensures the investigators will always have to go to the website each time they need a new form and so if there have been any updates to the CRFs the site staff will therefore always be using the latest versions.

The Investigator must ensure a separate CRF is printed off for each patient enrolled and that a photocopy is taken for their records prior to submitting data to the LCTU. The CRFs have been written following the LCTU Standard Operating Procedures.

The CRFs must be kept on file by the investigator and maintained in an up-to-date condition at all times. The investigator, or a designated sub-investigator, must sign and date the bottom of the CRFs, as indicated.

Any corrections will be made by the investigator, or designated staff, on the original forms before they are photocopied and the original submitted to the LCTU; this is to ensure that the corrections will also appear on the investigator's copy. All such corrections must be initialled and dated by the investigator, or designated staff, and the reason for the correction stated unless obvious. Any corrections needed after submission of the CRFs will be handled by way of Data Queries sent out by the LCTU.

Only medically qualified (sub-) investigators can sign off data on clinical assessments/safety. If the PI is unable to sign off the CRFs, e.g. they have left the hospital and are no longer employed by the institution, another similarly qualified person may then perform this task. This must be agreed to in writing by the Chief Investigator on the Site Delegation Log.

16.2. Data Handling

Data recorded on the CRFs will be entered into the CR-UK Liverpool Cancer Trials Unit MACRO database.

Systematic data validation is performed by the LCTU's Data Managers and the Trial Statistician to obtain a clean database prior to the statistical analysis. The ESPAC-4 Data Validation Plan will be executed following the LCTU SOPs for data management. A full Data Validation Report will be produced by the Data Manager and any issued resolved.

Data will be processed in accordance with the general terms and conditions of the authorisation from the 'Information Commissioner's Office' to CR-UK Liverpool Cancer Research Trials Unit, as required, according to national legislation implementing the Data Protection Directive; 95/46/EC.

17. Non-UK Protocols and Protocol Amendments

17.1. Non-UK Protocols

Each non-UK country participating in the study will have its own trial protocol and it will be given a country specific protocol identifier, which will include the country name, version number and date. For example, Sweden Version: 1 Date: 16/12/08.

When a co-sponsor or legal representative of a UK sponsor has been identified in each country and a (co-)sponsorship agreement has been signed, the current UK protocol will be issued to the country as Version 1. Any amendment of the protocol must adhere to the guidelines set out in section 16.2 and when a new version of the protocol has been approved by the relevant competent authority and the IEC a copy of the new version, relevant approvals, any supporting documentation and relating paperwork should be sent to the LCTU for their records.

17.2. Amendments

Deviations from the protocol should not occur.

Amendments are classified as changes made to a study after favourable ethical and regulatory opinion has been given. There are two types of amendment; substantial and non-substantial. In the ESPAC-4 trial the amendments have been further classified as per the table below:

Table 12.

	Details of Amendment/Change
Substantial Amendments	Change of main objectives of the trial
	Change in the design of the research
	Change to risk/benefit assessment
	Change in recruitment procedures
	Change in measures of efficacy
	Number of subjects
	Change in safety reporting and monitoring
	Duration of exposure/dose of Investigational Medicinal Product
	New toxicological or pharmacological data relevant to the trial
	Definition of the end of the trial
	Change of inclusion/exclusion criteria
	Schedule of samples
	Change to Patient Information Sheets / Consent Forms / GP Letter
	Questionnaires
	Change of Principal Investigators/sites or the addition of new sites/PIs
	Updates to the Investigator Brochure
Non-Substantial Amendments	Correction of typographical errors or minor clarifications
	Change in exploratory/tertiary end points
	Change in funding arrangements
	Change in the logistical arrangements for storing or transporting samples
	<10% increase to the study period
	Change in data capture forms

All substantial amendments would require approval/favourable opinion by the appropriate Competent Authority and IEC. Neither the investigator(s) nor CR-UK Liverpool Cancer Trials Unit will make any major changes to the Study Protocol without the written agreement from the Trial Steering Committee and the Chief Investigator. Minor changes can be made by an Investigator with approval from the CR-UK Liverpool Cancer Trial Unit and the Chief Investigator. Any admin changes can be made as required without prior notification to the LCTU or the Chief Investigator.

Substantial protocol amendments become effective when written approval has been provided by the Chief Investigator, the Director of CR-UK Liverpool Cancer Trials Unit, and approval/favourable opinion from Competent Authorities and/or IEC has been obtained as required.

18. Agreements

18.1. Research Site Agreement

Before the initiation of the clinical trial at a site, the arrangements between CR-UK Liverpool Cancer Trials Unit and investigator/institution as laid down in the Research Site Agreement must be confirmed in writing.

18.2. Co-sponsorship/International Agreements

Each country outside the UK participating in the study, must identify a suitable co-sponsor or legal representative of a UK sponsor and the delegation of duties between the UK (co-)sponsor and themselves must be confirmed in writing and laid down in the (Co-)Sponsorship Agreement.

19. Completion of Trial

19.1. Trial Completion Procedures

Investigators will be informed when patient recruitment is to cease.

Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained.

The ISDMC may recommend to the TSC that the trial be stopped prematurely. Such premature termination/suspension of trial will be notified to Regulatory Authorities and IECs as required.

19.2. Archiving of Trial Documents

The investigator at each research site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until CR-UK Liverpool Cancer Trials Unit informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

CR-UK Liverpool Cancer Trials Unit undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

At present according to ICH Guideline:

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. (ICH E6, 4.9.5)

20. Statistical Considerations

20.1. Introduction

An overview of the statistical considerations relevant for the trial is included. A single analysis plan will be developed prior to the first planned interim analysis. This analysis plan will contain all information required for all interim analysis and the final analysis of the data for both the ductal patients and the peri-ampullary patients. This document will be approved by the trial steering committee and an Independent Safety and Data Monitoring Committee (ISDMC). The main features of these planned statistical analyses are included here in the main protocol. Where statistical considerations for the ductal and peri-ampullary differ, separate sections are provided.

20.2. Randomisation Schedule

Minimisation will be implemented for the allocation of treatments using a specially designed computer program, with the following stratification factors:

(i) Resection margin status (negative or positive)
(ii) Country

Allocation to treatment arms will take place in the ratio 1:1. A random element is incorporated in the minimisation algorithm to prevent the remote chance of predictability.

Central randomisation, by fax, will be undertaken by the LCTU. This will allow the patient eligibility criteria to be scrutinised and removes the potential for selection bias by concealing the randomisation procedure from all recruiting clinicians and trial participants.

20.3. Blinding

The trial is open-labelled due to the different schedules of treatment administration. However, the primary end-point, overall survival, is objective removing the potential for observer bias.

20.4. Missing Data

Missing data will be closely monitored during the trial and its occurrence will be minimised by adopting the following strategy:

(i) A general CRF completion guideline document will be provided to each site and staff will be instructed to complete the CRF in accordance with this document.
(ii) A separate data management plan that will include instructions for checking missing data will be developed to give a detailed account of the procedures for data management.
(iii) Data from the CRF will be entered onto a MACRO database with extensive data validation checks alerting all missing data to be queried.
(iv) Central statistical data monitoring will summarise missing or inconsistent data periodically.
(v) If missing data occurs consistently for particular clinicians or sites this will be raised as a training issue.

Where missing data remain, as much information as possible will be collected about the reasons for missing data and this will be used to inform any imputation approaches employed for assessing robustness of results to missing data.

20.5. Statistical analysis plan

Analysis of the primary outcome, overall survival, will be from the time of randomisation to the time of death from any cause or the censor date. Survival analysis and final publication of these results will be carried out when all patients have a minimum of 2 years follow-up after randomisation.

Analysis will be carried out using a logrank test on an intention to treat basis. Cox proportional hazards modelling, or alternative, will be used to investigate and adjust any treatment effect by stratification factors and prognostic factors and assess the evidence for an interaction between treatment and resection margin. The proportion of grade 3/4 toxicity will be compared across treatments using Pearson's chi-square test with continuity correction or Fisher's Exact test.

Quality of life will be assessed over time and treatment groups compared using longitudinal analysis. Joint modelling or quality-adjusted survival analysis will be undertaken to allow a simultaneous assessment of quality of life and survival.

Survival data will also be analysed when all patients have been followed for 5 years to assess long-term treatment effects. All statistical analyses will be carried out on an intention to treat basis, retaining patients in their randomised treatment groups and including protocol violator and ineligible patients. A sensitivity analysis excluding any ineligible patients will also be conducted and reported.

20.6. Outcome Measures

20.6.1. Patients with Pancreatic Ductal Adenocarcinoma

Primary Outcome

Overall survival

The primary outcome measure is length of survival defined as number of days between date of randomisation and date of death due to any cause (event) or date of last follow-up if patient is still alive at time of analysis (censored).

Secondary Outcomes

The secondary outcome measures are:

1. Toxicity graded according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 3.0
2. Quality of Life (assessed using the EORTC QLQ C-30 v3)
3. Survival rate at 2 years
4. Survival rate at 5 years
5. Relapse free survival (RFS)

20.6.2. Patients with Peri-ampullary Carcinoma

Primary Outcome

Overall survival

The primary outcome measure is length of survival defined as number of days between date of randomisation and date of death due to any cause (event) or date of last follow-up if patient is still alive at time of analysis (censored).

Secondary Outcomes

The secondary outcome measures are:

1. Toxicity graded according to the National Cancer Institute common toxicity criteria (NCI-CTC) version 3.0
2. Quality of Life (assessed using the EORTC QLQ C-30 v3)
3. Survival rate at 4 years
4. Relapse free survival (RFS)

20.7. Sample Size Calculations

20.7.1. Patients with Pancreatic Ductal Adenocarcinoma

Sample size calculations were carried out using the ARTSURV package in Stata (Version 11).

The primary outcome measure is overall survival for gemcitabine compared to gemcitabine plus capecitabine. Oettle et al[9] have recently compared adjuvant gemcitabine against no postoperative anticancer therapy in patients undergoing complete, curative-intent resection of pancreatic cancer. They quote an estimated overall survival rate at 2 years of 47.5% in the gemcitabine group.

Recruiting 361 patients to each treatment arm (722 patients in total) will ensure that at the time of analysis, 480 deaths have been observed. A 0.05 level two-sided logrank test for equality of survival rates will then have 90% power to detect at least a 10% absolute improvement from an assumed 2-year survival probability of 0.475 on gemcitabine to at least 0.575 in the combination group.

This sample size has been inflated to account for both patient withdrawals (10%) and patients who are lost to follow-up (5%) at the time of analysis. Conservative values for both eventualities are used to ensure that enough deaths have been observed at the time of the final analysis and protect against and underpowered trial.

Final results from ESPAC-3(v2) comparing overall survival for Gemcitabine and 5FU confirm that a 2 year survival rate of 0.475 is appropriate. To assess the potential impact on power should the 2-year survival probability deviate from 0.475, a range of plausible values for gemcitabine are explored. The total sample size varies from 712 to 722 to 640, each for 90% power to detect at least a 10% absolute improvement in the combination group from an assumed 2-year survival probability of 0.42, 0.475, and 0.59 respectively. Therefore, should the actual survival probability deviate from 0.475 we would still have at least 90% power to detect the required 10% improvement with 361 patients per group.

For the secondary outcome of quality of life, the ESPAC-1 trial estimated the mean change from baseline to 6 months in global health status to be 14 points (95% CI 5 to 22) on chemotherapy (estimated standard deviation approximately 31 points based on a sample of 53 patients). These data suggest that 722 patients would give >99% power to detect a difference of at least 8 points in mean global health status change scores between gemcitabine and gemcitabine plus capecitabine using a t-test. It is likely there will be missing quality of life data at baseline and/or 6 months which will diminish the power to 98%, 97%, 94% and 90% assuming 20%, 30%, 40% or 50% missing data respectively.

20.7.2. Patients with Peri-ampullary Carcinomas

The primary outcome is overall survival for Gemcitabine plus Capecitabine compared to Gemcitabine alone. For the Gemcitabine-only arm, an overall 4 year survival proportion is given as 0.45. This is verified by the final results of the ESPAC-3 trial.

With a minimum of 370 patients per treatment group (740 with 404 deaths), a 0.05 level two sided logrank test for equality of survival rates will have a 80% power to detect at least a 10% absolute improvement from an assumed 4-year survival probability of 0.45 on Gemcitabine to at least 0.55 in the combination group.

To assess the potential impact on power should the 4-year survival probability deviate from 0.45, a range of plausible values for Gemcitabine are explored. The total sample size varies from 682 to 740 to 700, each for 90% power to detect at least a 10% absolute improvement in the combination group from an assumed 4-year survival proportion of 0.35, 0.45 and 0.55 respectively. Therefore, should the actual survival probability deviate from 0.45, we would still have at least 90% power to detect the required 10% improvement with 370 patients per group. All sample size calculations make an allowance for a drop-out rate of 5%

20.8. Patient Accrual

Recruitment will be organised through up to 8 different countries and 5 National Co-ordinating Centres with responsibilities that include co-ordinating patient randomisation through the LCTU.

20.8.1. Patients with Pancreatic Ductal Adenocarcinoma

The time period to recruit 722 patients is estimated to be a maximum of six years. The evidence that this recruitment rate is achievable comes from the ESPAC-3(v2) trial which recruited 1149 pancreatic ductal adenocarcinoma patients in 6 years, with an average monthly recruitment rate of 27 patients over the last 48 months.

The total duration of the study is expected to be approximately 11 years from the date the first patient is entered to the date of final (5 year) analysis. The trial will close after the last patient, last follow up visit.

20.8.2. Patients with Peri-ampullary Adenocarcinomas

The time period to recruit 740 patients is estimated to be a maximum of 3.5 years. This requires that over the last 24 months, an average of 22 patients per month be recruited. Including follow-up, the total duration of the study is expected to be 7 ½ years.

20.9. Analysis Plan

The trial will be analysed and reported following the 'CONSORT' guidelines[32].

All statistical analyses will be on an intention to treat basis, including all randomised patients (including protocol violator and ineligible patients) retained in their randomised treatment groups. A sensitivity analysis excluding any ineligible patients will also be conducted and reported.

Missing data, which is anticipated to mainly affect the quality of life outcome measure, will be handled by considering the robustness of the complete case analysis to sensitivity analyses using different imputation assumptions informed by data collected on reasons for missing data. A joint modelling approach where time to dropout is taken as the time to event outcome will also be explored.

Continuous variables will be summarised by descriptive statistics (mean, standard deviation, minimum, median and maximum) and frequency tables will be provided for categorical data, stratified by treatment arm in all cases.

20.10. Primary Outcome

The primary objective of the study is to determine whether the combination of Gemcitabine plus Capecitabine produces a survival advantage over Gemcitabine alone in patients with either pancreatic ductal adenocarcinoma or peri-ampullary carcinoma who have undergone 'curative' resection.

Survival curves will be estimated by the method of Kaplan and Meier[33] and compared across treatment groups with the logrank test at a two sided significance level of 0.05. The unadjusted hazard ratio and respective 95% confidence interval will be computed using the Cox proportional hazards regression model[34], or appropriate alternative. The stratification factors, resection margin and country, and other prognostic factors (involvement of the resection margin, tumour grade, tumour size, nodal involvement, CA19-9 and age) as appropriate, will be adjusted for in secondary analyses. The model will also be used to assess the evidence for a treatment-by-resection margin and treatment-by-country interaction. The underlying assumptions of any fitted model will be assessed as appropriate.

20.11. Secondary Outcomes

The incidence and severity of haematological, non-haematological and overall toxicity will be assessed. The incidence of any Grade 3 or 4 toxicities will be compared across treatment groups using Pearson's chi-square test with continuity correction or Fishers Exact test where appropriate.

For the quality of life outcome, characteristics of responders and non-responders will be compared and potential biases assessed. Quality of life will be assessed over time and treatment groups compared using longitudinal analysis with appropriate recognition for informative dropout. Joint modelling or quality-adjusted survival analysis will be undertaken to allow a simultaneous assessment of quality of life and survival.

Ductal patient group only: the survival probability and standard error will be estimated for each treatment group from the Kaplan-Meier survival curves at 2 and 5 years. The difference in survival probability between treatment groups will be calculated and presented with a 95% confidence interval for the difference at each time point.

Peri-ampullary patient group only: the survival probability and standard error will be estimated for each treatment group from the Kaplan-Meier survival curves at 4 years. The difference in survival probability between treatment groups will be calculated and presented with a 95% confidence interval for the difference.

Relapse free survival will be from the time of randomisation to the time of relapse or the censor date. Relapse will be determined using clinical and biochemical diagnosis (CA19-9). If present, a CT scan should be performed to confirm clinical suspicions in accordance with standard clinical practice. Relapse free survival curves will be estimated by the method of Kaplan and Meier[33] and compared across treatment groups with the logrank test at a two sided significance level of 0.05. The unadjusted hazard ratio and respective 95% confidence interval will be computed using the Cox proportional hazards regression model[34], or appropriate alternative.

20.12. Interim Analysis and Data Monitoring Committee

ESPAC-4 will be monitored by an independent Data Monitoring Committee (DMC) which will assess the trial data and take into account the current world-wide evidence. Analyses of trial data for the DMC review are initially planned at 6-monthly intervals for the first 2 years, to assess recruitment rates and toxicity. Analysis of the primary and secondary outcome measures by treatment group will be carried out on an approximate bi-annual basis when the required number of deaths is reached (see stopping guidelines). All interim analysis results will be confidential to the DMC members and will NOT be for review by the trial working group (except the trial statistician preparing the DMC report), Trial Steering Committee, investigators or collaborators.

The trial will be stopped or amended if sufficient evidence emerges that one or other treatment is clearly indicated or contra-indicated, as considered by the DMC in light of the analyses presented. Analyses will be reported to DMC members who will consider the data, including stopping guidelines (see stopping guidelines section), in a clinical context accounting for other emerging worldwide evidence and overall clinical relevance. DMC members will then make formal recommendations to the trial working group and TSC regarding the continuation of recruitment of patients into the study and will comply with a trial-specific DMC charter according to ICH GCP guidelines.

20.13. Stopping Guidelines

In order to carry out repeat significance tests in a conventional manner at each interim and final analysis, appropriate stopping guidelines must be employed to ensure that the overall significance level does not exceed the pre-specified type I error rate (5%) for the trial. The Peto method[35] will provide the stopping guidelines for 4 equally spaced interim analyses that are planned after approximately 100, 200, 300 and 400 deaths at a two-sided significance level of 0.001. The final analysis will be undertaken after the final patient has 2 years of follow-up (510 expected deaths) and will be conducted at a two-sided significance level of 0.05. This method was chosen for the conservative boundaries to ensure that interim results, which may have limited follow-up, would have to be extreme in order to be convincing to the clinical community before early termination is recommended. The Peto method also minimises controversy regarding interpretation of the final p-value which is assessed against the traditional significance level of 5%. No inflation factor needs to be applied to the sample size using this approach.

A futility analysis will also be carried out at each interim analysis. If the log rank statistic is negative at any of the interim analyses, the trial will be stopped due to futility.

The DMC will be asked to consider patient safety as well as treatment efficacy and as such will consider all outcome measures in their decision to stop or continue the trial. The stopping guidelines presented are in relation to the primary outcome measure but the trial may be terminated early by the DMC if there are serious concerns for patient safety without crossing the stopping boundaries set for the primary outcome measure of survival.

20.14. Reporting of results

20.14.1. Ductal patient group

The comparison of primary and secondary outcome measures between gemcitabine and gemcitabine combined with capecitabine will be undertaken and published when all patients have a minimum of 2 years follow-up, assuming the trial is not terminated early. To assess long-term effects, a further analysis and publication of results will be carried out when all patients have a minimum of 5 years follow-up.

20.14.2. Peri-ampullary patient group

The comparison of primary and secondary outcome measures between gemcitabine and gemcitabine combined with capecitabine will be undertaken and published when all patients have a minimum of 4 years follow-up, assuming the trial is not terminated early.

21. Use of information

All unpublished information relating to this study and/or to the Investigational Product(s), is considered confidential by the CR-UK Liverpool Cancer Trials Unit.

The investigator should understand and agree to that CR-UK Liverpool Cancer Trials Unit may use the information from this clinical trial in connection with the development of the product, and therefore, may disclose it as required to other investigators, to government licensing authorities, to regulatory agencies of other governments and commercial partners.

22. Publications

The Chief Investigator will be the primary author on all study publications, with recognition of the trial statistician, clinical/safety coordinator and the main trial co-ordinator associated with the trial. The named authors will be determined by the number of patients recruited on to the trial; as a guide in a large phase III study (ESPAC-4) 50 patients recruited at a site will receive at least one authorship. In the case of international studies there will be at least one representative from each country who provided recruitment, with high recruiters receiving pro-rota authorship. Where there are group collaborations within a country as far as possible each party will be given one author.

The total number of authors and the order on a manuscript will be determined by the ESPAC working group after the trial report has been presented. However this may ultimately be determined by the journal chosen for submission. All co-authors will be sent a draft paper to review and will agree the content before submission to any journal.

The Chief Investigator along with the ESPAC working group will decide on the strategy for oral communication. The initial presentation will be delivered by the Chief Investigator/Agreed Co-Investigator. Subsequent presentations are welcome by co-investigators to present the results in their own countries and organisations.

Investigators must undertake not to submit any part of their individual data for publication without the prior consent of the ESPAC working group.

23. Protocol Amendments

Version	Summary of Changes
Protocol v1 06/11/2007	Original
Protocol v2 13/02/2008	i) Updates to the inclusion and exclusion criteria. ii) Clarification of treatment administration. iii) Clarification of dose banding. iv) Instructions for the management of patients with renal impairment updated. v) Instructions for the management of patients with hepatic impairment updated. vi) Miscellaneous administrative changes.
Protocol v3 21/05/2008	i) Update of the exclusion criteria. ii) Randomisation procedure changed from stratification to minimisation. iii) Policy on receiving and storing Informed Consent Forms at the LCTU changed. iv) Miscellaneous administrative changes.
Protocol v4 18/08/2008	i) Update to the time points at which samples are taken for the translational study. ii) Clarification of time points for patient consent to be sought. iii) Update of the IMP section, clarifying packaging, labelling, ordering, dose banding. iv) Update of instructions for the management of toxicities. v) Update to the follow-up period for patients. vi) Update to translational study sample collection and storage. vii) Addition of section regarding non-UK protocols and amendments. viii) Addition of section regarding non-UK (co-)sponsorship agreements. ix) Miscellaneous administrative changes.
Protocol v5 26/03/2009	i) Update of inclusion criteria to allow patients up to 12 weeks post-op to enter the trial. ii) SAE terminology updated for consistency. iii) SAEs occurring prior to study treatment no longer need to be reported. iv) CRF and data handling updated – CRFs now available for download via the LCTU website. v) Miscellaneous administrative changes.
Protocol v6 21/01/2010	i) Updated rationale to reflect the publication of two large Phase III clinical trials in the disease area, the GemCap study and the 2 year survival analysis of the ductal patients from the ESPAC-3(v2) trial. ii) Revision of Investigational Medicinal Product (IMP) Section to allow the use of generic gemcitabine and capecitabine instead of only Gemzar and Xeloda respectively. iii) Addition of a window of 2 weeks from randomisation to start of study treatment. iv) Addition of phone call prior to reporting SAE by fax. v) Addition of futility analysis. vi) Updated ethical section to reflect the transfer of SSI assessment form LREC to local R&D departments vii) Updated list of trial personnel. viii) Clarification of inclusion criteria stating that a CT scan is required to assess whether a patient has metastases. ix) Updated protocol statements. x) Updated translational kit types. xi) Updated information regarding oversight committees and planned meetings. xii) Updated international study contacts. xiii) Miscellaneous administrative changes.

Protocol v7 21/07/2011	i) Reduction of target accrual from 1080 to 656 for the ductal patients following a review of the statistical methods of power. ii) Addition of peri-ampullary carcinomas to the inclusion criteria with a target accrual of 740. iii) Update of statistics section to reflect the new accrual target and addition of peri-ampullary patients. iv) Clarification of the inclusion criteria regarding the 12 week limit between surgery and randomisation. v) Update to the publication policy (section 22). vi) Update to the gemcitabine treatment for both arms to allow a +2 day window in the administration of the drug to account for public holidays and other miscellaneous reasons for minor delays. vii) If it is local practice, allow the FBC for measuring toxicity following each week of treatment to be taken up to 2 days prior so that the results are ready on days 1, 8 and 15. viii) Updates to the instructions for managing some toxicities (section 11) for clarification purposes. ix) Schedules of Study Procedures updated for clarity. x) Addition of details regarding the optional collection of pancreatic juice during surgery. xi) UICC version updated to 7th Edition (2009). xii) Updated international contacts. xiii) Miscellaneous administrative changes.
Protocol v8 04/04/2012	i) Peri-ampullary patient cohort: following CTAAC's review of protocol version 7, UK sites will not contribute *Extrahepatic bile ducts - distal (ICD-O C24.0)* or *Small intestine (ICD-O C17)* tumour patients to the peri-ampullary cohort. These restrictions do not apply to non-UK sites. ii) Inclusion criteria no. 1: specified tumour types and locations for both the ductal and peri-ampullary patient cohorts, as on page 2 of the randomisation form. iii) Inclusion criteria no. 8: allow for alternate methods to be used for calculating creatinine clearance, as long as the value is the equivalent of at least 50ml/min using the Cockcroft and Gault method. iv) Exclusion criteria no. 11 clarified following queries from site staff: the *baseline* neutrophil count cannot be less than $1.5x10^9$/l; it may of course become lower during treatment but that does not mean the patient should be necessarily withdrawn from treatment. v) Exclusion criteria no. 12 clarified following queries from site staff: the *baseline* platelet count cannot be less than $100x10^9$/l; it may of course become lower during treatment but that does not mean the patient should be necessarily withdrawn from treatment. vi) 'Thrombocyte' renamed 'platelet' for consistency. vii) Clarification of section 11.5.2.2, stating that patients with renal impairment should be withdrawn from trial *treatment* and not from the study as a whole. viii) Section 12.7: clarification of patient procedures regarding the discontinuation of treatment and withdrawal from the trial. ix) Section 13: additional details regarding safety reporting by both the sites and the LCTU. xiv) Miscellaneous administrative changes.
Protocol v9 07/01/2014	i) Update of the ductal cohort's target accrual to 722, following the ISDMC's review of the patient withdrawal rate. ii) Minor updates to the study schedules (tables 9 and 10) for clarity. iii) Addition of section 13.3.5, Reference Safety Information. iv) Updated statistics section 20.7.1 to reflect the accrual change. v) Miscellaneous administrative changes.

24. Contact numbers for the randomisation centre and national coordinating centres

Liverpool UK	Karl Harvey LCTU	Tel: +44 (0) 151 794 8932 / 8873 Fax: +44 (0) 151 794 8247 / 8930 / 8931 Email: Karl.Harvey@Liverpool.ac.uk
Stockholm Sweden	Anna-Lena Johansson Karolinska University Hospital	Tel: +46 (0) 8 517 736 41 Fax: +46 (0) 8 30 69 89 Email: Anna-Lena.S.Johansson@Karolinska.Se
Paris France	Dominique Notelet GERCOR Group	Tel: +33 (0) 1 40 29 85 01 Fax: +33 (0) 1 40 29 85 08 Email: Dominique.Notelet@Gercor.com.fr
Heidelberg Germany	Claudia Trierweiler University of Heidelberg	Tel.: +49 (0) 6221 56 5096 Fax: +49 (0) 6221 56 5863 Email: Claudia.Trierweiler@NCT-Heidelberg.De
Mumbai India	Bhawna Sirohi Tata Memorial Centre	Tel: +91 9930 033 980 Fax: Email: Bhawna.Sirohi@BTInternet.com
Bologna Italy	Donatella Di Piazza Bologna University	Tel: + Fax: + Email: D.Donatella@gmail.com

APPENDIX 1. References

1. http://info.cancerresearchuk.org/cancerstats/

2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59(4):225-49.

3. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. Eur J Cancer, 2001; 37: S4-S66.

4. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. Br J Surg. 2004;91:1410-2.

5. Shaib Y, Davila J, Naumann C, El-Serag H The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. Am J Gastroenterol. 2007 ;102:1377-82.

6. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg. 2004;91:586-94.

7. Neoptolemos J, Stocken D, Freiss H, et al. A randomised trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-1210.

8. Bakkevold K, Arnesjo B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater-results of a controlled, prospective, randomised multicentre study. Eur J Can 1993;29A(5):698-703.

9. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gall bladder carcinoma? A phase III multicentre prospective randomised controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002;95(8):1685-1695.

10. Kosuge T, Kiuchi T, Mukai K, Kakizoe T. A multicenter randomised controlled trial to evaluate the effect of adjuvant cisplatin and 5-Fluorouracil therapy after curative resection in cases of pancreatic cancer. Jpn J Clin Oncol 2006;36(3):159-165.

11. Neoptolemos J, Dunn J, Stocken D, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358(9293):1576-1585.

12. Klinkenbijl J, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region. Ann Surg 1999;230(6):776-784.

13. Smeenk HG, Van Eijck CHJ, Hop WC, Erdmann J, Tran KCK, Debois M, Van Cutsem E, Van Dekken H, Klinkenbijl JH, Jeekel JH. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC Trial 40891. Ann Surg 2007; 246: 734-740.

14. Kalser M, Ellenberg S. Pancreatic cancer: adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899-903.

15. Douglass H. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer 1987;59:2006-2010.

16. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Kudrimoti MR, Fromm ML, Haddock MG, Schaefer P, Willett CG, Rich TA. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008; 299(9):1019-26.

17. Twombly R. Adjuvant chemoradiation for pancreatic cancer: few good data, much debate. J Natl Cancer Inst. 2008;100(23):1670-1.

18. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007 Jan 17;297(3):267-77.

19. Neuhaus P, Riess H, Post S, Gellert K, Ridwelski K, Schramm H, Zuelke C, Fahlke J, Langrehr J, Oettle H and the Deutsche Krebsgesellschaft (CAO/AIO). CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with gemcitabine versus observation in patients with resected pancreatic cancer (PC). J Clin Oncol 2008; 26, Supplement 15S: Abstract LBA4504.

20. Neoptolemos J, Büchler M, Stocken DD, Ghaneh P, Smith D, Bassi C, Moore M, Cunningham D, Dervenis C, Goldstein D. ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma. J Clin Oncol 2009; suppl 18s: 27; Abstract LBA4505.

21. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W; National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007;25(15):1960-6.

22. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine (G) plus Capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). J Clin Oncol 2005; 23: No. 16S 4010.

23. Sultana A, Tudur Smith C, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007 25(18):2607-15.

24. Sultana A, Ghaneh P, Cunningham D, Starling N, Neoptolemos JP, Smith CT. Gemcitabine based combination chemotherapy in advanced pancreatic cancer-indirect comparison. BMC Cancer. 2008 Jul 8;8:192.

25. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2009; 27(33): 5513-8.

26. Stocken D, Büchler M, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer. 2005; 92(8): 1372-81.

27. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Büchler MW. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009; 100(2): 246-50.

28. Kloppel G, Hruban RH, Longnecker DS, et al. Ductal adenocarcinoma of the pancreas. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours. Pathology and genetics of tumours of the digestive system. Lyon7 IARC Press; 2000. p. 221- 30.

29. Morris-Stiff G, Alabraba E, Tan YM, Shapey I, Bhati C, Tanniere P, Mayer D, Buckels J, Bramhall S, Mirza DF Assessment of survival advantage in ampullary carcinoma in relation to tumour biology and morphology. Eur J Surg Oncol. 2009 ;35:746-50.

30. Henson DE, Schwartz AM, Nsouli H, Albores-Saavedra J. Carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla of vater share a field for carcinogenesis: a population-based study. Arch Pathol Lab Med 2009 ;133:67-71.

31. Albores-Saavedra J, Schwartz AM, Batich K, Henson DE . Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. J Surg Oncol. 2009 ;100:598-605.

32. Hatzaras I, George N, Muscarella P, Melvin WS, Ellison EC, Bloomston M Predictors of survival in periampullary cancers following pancreaticoduodenectomy. Ann Surg Oncol. 2010 ;17:991-7.

33. Winter JM, Cameron JL, Olino K, Herman JM, de Jong MC, Hruban RH, Wolfgang CL, Eckhauser F, Edil BH, Choti MA, Schulick RD, Pawlik TM. Clinicopathologic analysis of ampullary neoplasms in 450 patients: implications for surgical strategy and long-term prognosis. J Gastrointest Surg. 2010 ;14:379-87.

34. Kimura W, Futakawa N, Yamagata S, Wada Y, Kuroda A, Muto T, Esaki Y: Different clinicopathologic findings in two histologic types of carcinoma of papilla of Vater. Jpn J Cancer Res 1994,85:161-166.

35. Westgaard A, Tafjord S, Farstad IN, Cvancarova M, Eide TJ, Mathisen O, Clausen OP, Gladhaug IP. Pancreatobiliary versus intestinal histologic type of differentiation is an independent prognostic factor in resected periampullary adenocarcinoma. BMC Cancer. 2008 ;8:170.

36. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010 ;362:1273-81.

37. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald A, Carter R, Tebbutt NC, Dervenis C, Smith D, Glimelius B, Coxon FY, Lacaine F, Middleton MR, Ghaneh P, Bassi C, Halloran C, Oláh A, Rawcliffe CR, Büchler MW. Ampullary cancer ESPAC-3 (v2) trial: A multicenter, international, open-label, randomized controlled phase III trial of adjuvant chemotherapy versus observation in patients with adenocarcinoma of the ampulla of Vater. J Clin Oncol 29: 2011 (suppl; abstr LBA4006).. 2010 8;304:1073-81.

38. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2009 ;54:337-47.

APPENDIX 2. WHO Performance Status

WHO PERFORMANCE STATUS

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable only of limited self care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry out any self care; totally confined to bed or chair.

5 Dead.

APPENDIX 3. EORTC QLQ-C30 (version 3)

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
16. Have you been constipated?	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
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 4. Pre-Surgery Patient Information Sheet (V4 Date: 21/07/11)

PRE-PANCREAS SURGERY SAMPLE COLLECTION
PATIENT INFORMATION SHEET

You have been invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others if you wish.

- Part 1 tells you the purpose of the study and what will happen to you if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1

We would like to explain a little about the research being carried out at this institution and by our collaborators throughout Europe and then ask if you would like to take part. We would like to approach **ALL** patients undergoing pancreatic surgery to ask if they would help us with our research, The decision to talk to you is not based on any particular aspect of your condition and we have not consulted your medical records in making this decision. This decision does **NOT** imply anything about your condition.

What is the purpose of the trial?

The study involves the collection and subsequent storage of frozen tissue, pathological specimens, blood and urine samples.

Our goal is to gain a better understanding of pancreatic diseases including the genetic and molecular basis of pancreatic cancer. Cancer is caused by genes that you may already carry, or that accumulate in the cells of the pancreas for reasons that we do not fully understand. This could lead to earlier detection of the disease and to the development of more effective treatments.

We ask your permission to collect and store blood and urine samples before your operation in addition to keeping small pieces of the tumour once it has been removed. If the tumour is found to be malignant, from these samples, it will be possible to conduct future research to obtain more information about what causes cancers to form in the pancreas and to identify improved methods of earlier diagnosis. We also hope to be able to find out which types of tumour will be most sensitive to subsequent chemotherapy treatment in order to offer patients the most appropriate treatment after their surgery. As part of current and future research, the Cancer Research UK Liverpool Cancer Trials Unit may need access to some of this tissue and it will be stored in the University of Liverpool's laboratory.

Why have I been chosen?

As your doctor will already have discussed with you, your planned operation will involve removal of part (or all) of the pancreas for a presumed tumour. This tumour may arise from the pancreas itself or from part of the bile duct or ampulla which are both connected to the pancreas. Subsequent

pathological examination of the tumour once it is removed will definitively confirm whether the tumour is malignant (i.e. cancerous) and what type of cancer is present. If cancer is confirmed, you may be offered the option to go on to have chemotherapy once you have recovered from your operation.

Do I have to take part?

No. It is up to you decide whether or not to take part. If you do you will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me during the collection of the pre-surgery samples?

Blood tests

We would like your permission to take a 16.5ml blood sample from you, prior to surgery, for use in scientific studies investigating pancreatic cancer.

Urine tests

We would also like your permission to take a urine sample from you. The collection will be taken after fasting on the morning before your surgery. The nurse will give you a container to use for this. These urine tests will be used in scientific studies investigating pancreatic cancer.

Tissue samples

In order to gain a better understanding of the disease, we wish to collect and store specimens of your normal tissue and cancer tissue during your surgery to remove your pancreatic cancer.

What are the possible benefits of taking part?

Although there are no direct benefits to you for providing the samples described, the information we get from this study may help us to improve the future treatment of patients with pancreatic or peri-ampullary cancers.

What are the possible disadvantages and risks of taking part?

There are no possible risks or disadvantages of taking part, apart from slight discomfort during collection of the blood sample.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my participation in this study be kept confidential?

Yes. All information which is collected about you during the course of this research will be kept strictly confidential. With your permission we will inform the Liverpool Cancer Trials Unit (co-ordinating centre) of your participation in the study. Apart from these mentioned circumstances, any information about you that leaves the hospital will have your name and address removed so you cannot be identified from it.

Contact for Further Information

Should you have any further queries regarding this study or about any of the treatments described above:

Please feel free to ask your doctors any questions about the study or about any of the treatments described above.

Please contact _____
Name and Title

On tel. no. _____

Or contact _____
Name and Title

On tel. no. _____

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What will happen if I don't want to carry on with the study?

It is your decision whether you consent to take part in this study.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you (if appropriate).

In the event of defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from Cancer Research UK or their collaborators who are also involved in organising this research project. They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site and Liverpool Cancer Trials Unit.

Data collected during the study may be transferred for the purpose of analysis/registration within or outside the European Economic Area. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law. We will take all reasonable steps to protect your privacy.

Involvement of the general practitioner / family doctor (GP)

A copy of your consent form will be placed in your case notes so any other medical practitioners who treat you will be aware you have had samples taken. Your GP will not be informed of sample collection.

What will happen to any samples I give?

Some of your samples will be analysed at your hospital for the purpose of your treatment.

With your permission, we would like to transfer the 16.5ml blood samples, the urine samples and the tissue samples we take from you to the University of Liverpool and store them there. The researchers at the University of Liverpool work closely with other scientists around Europe and, with your permission, your samples may be transferred to these research collaborators for use in future scientific studies. These samples will be used only for investigating pancreatic cancer and will not be used for any commercial purposes.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

Your sample will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good research reason to do so. We will maintain this information so that we can properly manage the samples donated. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

Will any genetic tests be done?

The pancreas can release cells into the blood stream and we would like to use the 16.5ml blood sample to look at the genes from these cells. Cancer is caused by genes that you may already carry, or that accumulate in the cells of the pancreas for reasons that we do not fully understand. Our goal is to understand the genetic and molecular basis of pancreatic cancer. This could lead to earlier detection of the disease and to the development of more effective treatments, which may lead to a cure and possible prevention of the disease.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published to make them available to the public. They may also be used to apply to the regulatory authorities to make the drug widely available. You will not be named or identified in any publication.

Who is organising and funding this research?

This research project is funded by Cancer Research UK; they are supporting this study by providing core funding for staff to co-ordinate this trial. It is being sponsored by the Royal Liverpool and Broadgreen University Hospital NHS Trust and the University of Liverpool.

Your doctor will not receive any payment for including you in this study.

Who has reviewed the study?

The study has been reviewed for scientific content by members of the Cancer Research UK peer review committee and a Multi-Centre Research Ethics Committee has reviewed the study for ethical considerations. The trial has the support of the National Cancer Research Institute.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

APPENDIX 5. Pre-Surgery Sample Collection Patient Consent Form (V4 Date: 29/04/13)

PRE-PANCREAS SURGERY SAMPLE COLLECTION PATIENT CONSENT FORM

Name of Researcher: _____

Please initial

1. I confirm that I have read and understand the information sheet dated …… (version .....) describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes and data collected during the study, may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I give permission for the samples of my blood, urine, frozen samples and stored pathological specimens to be used for this trial and for future pancreatic cancer research. ☐
5. I give permission for my stored pathological specimens to be used for future pancreatic or peri-ampullary cancer research and be transferred to research institutes in the UK and rest of the world. ☐
6. I give permission for a copy of my consent form to be sent to the Liverpool Cancer Trials Unit (where it will be kept in a secure location), to allow confirmation that my consent was given. ☐
7. I am happy for the future publication and dissemination of research involving my gifted sample, which may contain genetic information. ☐
8. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Three copies required: one for patient, one for researcher and one for hospital case notes.

APPENDIX 6. Patient Information Sheet (Version: 6 Date: 21/07/11)

PATIENT INFORMATION SHEET AND CONSENT FORM

ESPAC-4: combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers.

You have been invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and talk to others if you wish.

- Part One tells you the purpose of the study and what will happen to you if you take part
- Part Two gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1

What is the purpose of the trial?

This study has been designed to find out whether one type of drug (chemotherapy) is more beneficial than a combination of two drugs when given after operation for patients with your condition.

Although the growth in your pancreas has been removed, there is a chance that you could develop further growths sometime in the future. Giving extra treatment with chemotherapy may stop this happening, ***but nobody knows for certain whether it is best to use a single drug or a combination of drugs.***

We have, therefore, designed a study to find whether there is any difference between two different types of chemotherapy treatment. If you agree to take part, you will be randomly allocated to one of two groups:

1) Gemcitabine
2) Gemcitabine & capecitabine

This means that half of all patients will be given gemcitabine alone and half will be given gemcitabine plus capecitabine. Therefore whether you are treated with one or other type of chemotherapy drug, the group will be decided by chance. Whichever group you are allocated you will be monitored closely.

Why have I been chosen?

You have one of two conditions: adenocarcinoma of the pancreas which is commonly referred to as pancreatic cancer, or peri-ampullary carcinoma. Your tumour has been removed, but extra treatment with drugs after surgery may stop further growths developing in the future. There will be 1396 patients taking part in the trial.

Do I have to take part?

No. It is up to you decide whether or not to take part. If you do you will be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me during the trial?

The chemotherapy treatments are with drugs called gemcitabine or alternatively gemcitabine plus capecitabine. All treatments are given in the outpatient clinic, so you do not need to be admitted to hospital. In the case of gemcitabine alone, this is given as an injection in to a vein in your arm once a week for three weeks out of four. Each gemcitabine visit will last about 2 hours. This will continue for a period of six months, so you will have six courses of treatment.

If you are to be treated with gemcitabine and capecitabine you will receive the gemcitabine as described above, however you will also take capecitabine. Capecitabine is a tablet which you will need to take this twice a day at home. You will also need to take capecitabine tablets for twenty-one days followed by a seven-day rest period (no medicine). After the seven day rest, you will continue taking the capecitabine tablets for 21 out of every 28 days.

After you stop receiving study treatment you will be required to attend hospital for a follow-up visit every 3 months, up to 60 months after entering the trial. During this visit you will have an examination and standard blood tests.

A very important aspect of this study involves assessing how your disease or any treatment you receive affects the quality of your life, so our research nurses will ask you to fill in a questionnaire that asks about how you are feeling and what activities you are able to undertake. This questionnaire will be repeated when you consent to enter the study and then at 3, 6, 12, 18 and 24 months afterwards, followed by annual assessments up to five years. The questionnaires will be completed when you attend for your treatment or follow-up appointments. It is very important for you to answer all the questions in the questionnaires for us to accurately assess the impact of the disease and treatment upon you.

Throughout the study you will be asked to provide different samples for you doctor to assess your health and treatments. We are also requesting some extra samples for scientific research. The extra samples are voluntary and you should indicate on your consent form if you are happy for these to be taken.

Blood tests
You will have blood samples taken for standard blood tests every time you attend for treatment. These blood tests are essential for your research doctor to be able to tell if you are well enough for your treatment.

In addition if you have given consent we would like your permission to sometimes take other blood samples from you for use in scientific studies investigating pancreatic and peri-ampullary cancers. You may have had a blood sample taken, with your approval, before your surgery. In addition we would like to take a approximately 16.5ml blood sample when you attend clinic before your first chemotherapy treatment and after your third month of treatment. If, at any point through the trial, you do not want to have this blood test you can tell your doctor and it will not affect your taking part in the trial.

Urine tests

We would also like your permission and consent to sometimes take urine samples from you. In addition to the collection which may have been taken after fasting on the morning before your surgery, a urine sample will be collected when you attend clinic before your first chemotherapy treatment and for your third month of treatment. The nurse will give you a container to use for this. These urine tests will be used in scientific studies investigating pancreatic cancer and we will ask you to provide consent for us to take these. If, at any point through the trial, you do not want to provide this urine test you can tell your doctor and it will not affect your taking part in the trial.

What are the alternatives for treatment?

If you decide not to participate in the study, then your doctor will discuss other options with you, for example, standard chemotherapy or no adjuvant treatment (surgery alone).

Are there any side-effects associated with these treatments?

Both gemcitabine and capecitabine can cause side effects which may include:

1. Sore mouth – you may be given a mouthwash in an attempt to prevent this.
2. Diarrhoea – this is usually mild but if persistent, tablets will be provided to relieve this.
3. Sore hands and feet – you will be given medication to correct this if this occurs.
4. Nausea and vomiting – this is usually mild and controllable with anti-sickness drugs.
5. Flu-like symptoms – you may have muscle aches and pains and a temperature. Paracetamol usually controls this.
6. Lowering of the blood count - this usually does not cause symptoms but increases the risk of getting infections, bruising and bleeding. You may rarely need to be admitted to hospital if this occurs and sometimes blood cell transfusions are necessary.
7. Chest pain has been reported but is uncommon.
8. Thinning of hair – this is unusual, but if it occurs the hair grows back shortly after the chemotherapy is stopped.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients with pancreatic and peri-ampullary cancers.

What are the possible disadvantages and risks of taking part?

As part of the study you will undergo at least one CT scan and possibly additional scans if required. The dose of radiation that you will receive could be equivalent to several decades' worth of natural background radiation. The National Radiological Protection Board described a few years' natural background radiation as 'Low Risk'. However, you would receive the same dose from the CT scans in this trial that is given to many patients with a similar condition as part of routine care in the NHS (UK).

Chemotherapy treatment might harm the unborn child therefore you should not take part in this trial if you are pregnant, breast-feeding or you intend to become pregnant during the study. If you are a woman who might become pregnant, or a man who has a partner of child bearing age, you must agree to use a reliable form of contraception during the trial i.e. two forms of contraception, one of which must be a condom. This should be continued for one year following treatment. If you or

your partner should become pregnant during the course of the study, you must tell your study doctor **immediately**.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in this study be kept confidential?

Yes. All information which is collected about you during the course of this research will be kept strictly confidential. With your permission we will inform your GP and the Liverpool Cancer Trials Unit (the co-ordinating centre) of your participation in the study. Other than this, any information about you that leaves the hospital will have your name and address removed so you cannot be identified from it.

Contact for Further Information

Should you have any further queries regarding this study or about any of the treatments described above:

Please feel free to ask your doctors any questions about the study or about any of the treatments described above.

Please contact _____
Name and Title

On tel. no. _____

Or contact _____
Name and Title

On tel. no. _____

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw then your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?

You can withdraw from treatment at any time but we would like you to still attend for follow-up visits every 3 months. If you do not wish to continue attending hospital, we would be grateful if you would allow us keep in touch with your General Practitioner to let us know your progress. If you withdraw, information collected may still be used if you allow. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this trough the NHS Complaints Procedure. Details can be obtained from the hospital.

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you (if appropriate).

In the event of a defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons from Cancer Research UK or their collaborators who also involved in organising this research project. They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site or the Liverpool Cancer Trials Unit.

Data collected during the study may be transferred for the purpose of analysis/registration within or outside the European Economic Area. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law. We will take all reasonable steps to protect your privacy.

Involvement of the general practitioner / family doctor (GP)

With your consent, your GP will be informed of your involvement in the trial. Any other medical practitioners who treat you, e.g. should you be admitted to hospital for any reason, will also be informed.

What will happen to any samples I give?

Some of your samples will be analysed at your hospital for the purpose your treatment.

With your permission, we would like to transfer the blood samples and the urine samples we take from you to the University of Liverpool and store them there. The researchers at the University of Liverpool work closely with other scientists around Europe and, with your permission, your samples may be transferred to these research collaborators for use in future scientific studies. These samples will be used only for investigating pancreatic and peri-ampullary cancers and will not be used for any commercial purposes.

The samples will be kept in a secure place until we need them; nobody outside of the study will have access to **any** confidential information that you give to us. Confidential details (such as your name, address and GP details) will be kept locally and not made available to collaborators.

Your sample will be coded and the researchers carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good research reason to do so. We will maintain this information so that we can properly manage the samples donated. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of tests.

Will any genetic tests be done?

The pancreas can release cells into the blood stream and we would like to use the larger blood sample to look at the genes from these cells. Cancer is caused by genes that you may already carry, or that accumulate in the cells of the pancreas for reasons that we do not fully understand. Our goal is to understand the genetic and molecular basis of pancreatic cancer. This could lead to earlier detection of the disease and to the development of more effective treatments, which may lead to a cure and possible prevention of the disease.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published to make them available to the public. They may also be used to apply to the regulatory authorities to make the drug widely available. You will not be named or identified in any publication.

Who is organising and funding this research?

This research project is funded by Cancer Research UK; they are supporting this study by providing core funding for staff to co-ordinate this trial. It is being sponsored by the Royal Liverpool and Broadgreen University Hospital NHS Trust and the University of Liverpool.

Your doctor will not receive any payment for including you in this study.

Who has reviewed the study?

The study has been reviewed for scientific content by members of the Cancer Research UK peer review committee and a Multi-Centre Research Ethics Committee has reviewed the study for ethical considerations. The trial has the support of the National Cancer Research Institute.

Thank you for taking the time to read and consider this information sheet. Should you decide to take part in the study, you will be given a copy of the information sheet and a signed consent form to keep.

APPENDIX 7. Patient Consent Form (Version: 5 Date: 07/01/14)

PATIENT CONSENT FORM (please read carefully)

ESPAC-4: combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers.

Name of Researcher: _____

	Please initial
1. I confirm that I have read and understand the information sheet, dated …… (version .....), describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.	
3. I understand that sections of my medical notes and data collected during the study, may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	
4. I **DO** give permission for the samples of my blood, and urine to be taken and used for this trial and for future pancreatic research and be transferred to research institutes in the UK and rest of the world. **[ONLY INITIAL IF YOU AGREE]**	
5. I **DO** give permission for my stored pathological specimens to be used for this trial and for future pancreatic research and be transferred to research institutes in the UK and rest of the world. **[ONLY INITIAL IF YOU AGREE]**	
6. I give permission for a copy of my consent form to be sent to the Liverpool Cancer Trials Unit (where it will be kept in a secure location), to allow confirmation that my consent was given.	
7. I am happy for the future publication and dissemination of research involving my gifted sample, which may contain genetic information.	
8. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study.	
9. I agree to take part in the above study.	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Three copies required: one for the patient, one for the researcher and one for hospital case notes.

APPENDIX 8. UICC 7th Edition (2009) TNM Classifications

Pancreas
(ICD-O C25)

Rules for Classification

The classification applies to carcinomas of the exocrine pancreas and pancreatic neuroendocrine tumours including carcinoids. There should be histological or cytological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories: Physical examination, imaging, and/or surgical exploration

N categories: Physical examination, imaging, and/or surgical exploration

M categories: Physical examination, imaging, and/or surgical exploration

Anatomical Subsites

C25.0	Head of pancreas[1]
C25.1	Body of pancreas[2]
C25.2	Tail of pancreas[3]
C25.3	Pancreatic duct
C25.4	Islets of Langerhans (endocrine pancreas)

Notes:
1. Tumours of the head of the pancreas are those arising to the right of the left border of the superior mesenteric vein. The uncinate process is considered as part of the head.
2. Tumours of the body are those arising between the left border of the superior mesenteric vein and left border of the aorta.
3. Tumours of the tail are those arising between the left border of the aorta and the hilum of the spleen.

Regional Lymph Nodes

The regional lymph nodes are the peripancreatic nodes, which may be subdivided as follows:

Superior	Superior to head and body
Inferior	Inferior to head and body
Anterior	Anterior pancreaticoduodenal, pyloric (for tumours of head only), and proximal mesenteric
Posterior	Posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
Splenic	Hilum of spleen and tail of pancreas (for tumours of body and tail only)
Coeliac	(for tumours of head only)

TNM Clinical Classification

T - Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ*
T1	Tumour limited to pancreas, 2cm or less in greatest dimension
T2	Tumour limited to pancreas, more than 2cm in greatest dimension
T3	Tumour extends beyond pancreas, but without involvement of coeliac axis or superior mesenteric artery
T4	Tumour involves coeliac axis or superior mesenteric artery

Note: *Tis also includes the 'PanIN-III' classification.

N - Regional Lymph Nodes

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

M - Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

Note: The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone. (The use of MX may result in exclusion from staging).

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 10 or more lymph nodes.
If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pM – Distant Metastasis*

pM1 Distant metastasis microscopically confirmed

Note: *pM0 and pMX are not valid categories

Residual Tumour (R) Classification*

The absence or presence of residual tumour after treatment is described by the symbol R. More details can be found in the TNM Supplement (International Union Against Cancer (UICC). *TNM Supplement. A Commentary On Uniform Use*, 3rd ed. Wittekind CH, Henson DE, Hutter RVP, et al., eds. New York; Wiley; 2003).

TNM and pTNM describe the anatomical extent of cancer in general without considering treatment. They can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. The definitions of the R categories are:

RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Note: *Some consider the R classification to apply only to the primary tumour and its local or regional extent. Others have applied it more broadly to include distant metastasis. The specific usage should be indicated when the R is used.

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Summary

Pancreas	
T1	Limited to pancreas ≤2cm
T2	Limited to pancreas >2cm
T3	Beyond pancreas
T4	Coeliac axis or superior mesenteric artery
N1	Regional

Ampulla of Vater
(ICD-O C24.1)

Rules for Classification

The classification applies only to carcinomas. There should be histological or cytological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories: Physical examination, imaging, and/or surgical exploration

N categories: Physical examination, imaging, and/or surgical exploration

M categories: Physical examination, imaging, and/or surgical exploration

Regional Lymph Nodes

The regional lymph nodes are:

Superior	Superior to head and body of pancreas
Inferior	Inferior to head and body of pancreas
Anterior	Anterior pancreaticoduodenal, pyloric, and proximal mesenteric
Posterior	Posterior pancreaticoduodenal, common bile duct, and proximal mesenteric

Note: The splenic lymph nodes and those of the tail of the pancreas are *not* regional; metastases to these lymph nodes are coded M1.

TNM Clinical Classification

T - Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to ampulla of Vater or sphincter of Oddi
T2	Tumour invades duodenal wall
T3	Tumour invades pancreas
T4	Tumour invades peripancreatic soft tissues, or other adjacent organs or structures

N - Regional Lymph Nodes

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

M - Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 10 or more lymph nodes.
If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

pM – Distant Metastasis*

pM1 Distant metastasis microscopically confirmed

Note: *pM0 and pMX are not valid categories

Residual Tumour (R) Classification*

The absence or presence of residual tumour after treatment is described by the symbol R. More details can be found in the TNM Supplement (International Union Against Cancer (UICC). *TNM Supplement. A Commentary On Uniform Use*, 3rd ed. Wittekind CH, Henson DE, Hutter RVP, et al., eds. New York; Wiley; 2003).

TNM and pTNM describe the anatomical extent of cancer in general without considering treatment. They can be supplemented by the R classification, which deals with tumour status after treatment. It reflects the effects of therapy, influences further therapeutic procedures and is a strong predictor of prognosis. The definitions of the R categories are:

RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Note: *Some consider the R classification to apply only to the primary tumour and its local or regional extent. Others have applied it more broadly to include distant metastasis. The specific usage should be indicated when the R is used.

G Histopathological Grading

GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Summary

Ampulla of Vater	
T1	Ampulla or sphincter of Oddi
T2	Duodenal wall
T3	Pancreas
T4	Beyond pancreas
N1	Regional

APPENDIX 9. Extent of Resection

Extent of Resection

Standard	Regional lymphadenectomy around the duodenum and pancreas. For head of pancreas the following lymph node groups are removed en-bloc: right side $12b_1$, $12b_2$, 12c; 13a, 13b; 14a, 14b; 17a, 17b; and separately 8a.
Radical	Regional lymphadenectomy as above plus (i) skeletonization of the common and proper hepatic arteries, superior mesenteric artery between aorta and inferior pancreatoduodenal artery, coeliac trunk; and (ii) dissection of the anterolateral aspect of the aorta and the inferior vena cava including Gerota's fascia. For head of pancreas the lymph nodes are removed en-bloc: as for standard pancreatic resection plus all 8; 9; all 12; all 14; $16a_2$, $16b_1$.
Extended Radical	Radical lymphadenectomy as above plus clearance of anterior aorta between the diaphragmatic hiatus (around the coeliac trunk) and the origin of the common iliac arteries. For head of pancreas the following lymph nodes are removed en-bloc: as for radical pancreatic resection plus clearance of all JPS Group16 lymph nodes.

Based on the Japanese Pancreatic Society lymph node numbering system.

PLEASE REFER TO FULL REFERENCE FOR FURTHER DETAILS:

Pedrazzoli S et al., Dig Surg 1999:16; 337-45.

APPENDIX 10. New York Heart Association Functional Classification

NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Definition
I.	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, or dyspnoea.
II.	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, or dyspnoea.
III.	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, or dyspnoea.
IV.	Unable to carry on any physical activity without symptoms. Symptoms are present even at rest. If any physical activity is undertaken, symptoms are increased.

APPENDIX 11. SAE Form (Version: 6 Date: 11/08/2010)

SSES4_D018/6, Date: 11/08/2010

ESPAC-4

European Study Of Adjuvant Chemotherapies In Resectable Pancreatic Cancer

Serious Adverse Event Form (Page 1)

E	S	P	A	C	4

PROJECT

TRIAL NUMBER

PATIENT INITIALS

All follow-up information MUST be added to THIS form.

Please complete an adverse event form for each SERIOUS Adverse Event (SAE) that the subject experiences

Centre No.: __ __ - __ __ Principal Investigator: _____

Date initial report sent to Liverpool Cancer Trials Unit: __ __ / __ __ __ / __ __ __ __ *(dd/mon/yyyy)*

☐ Initial Report

☐ Follow-up Report

LCTU Stamp

Section A: PATIENT INFORMATION

Gender: ☐ Male ☐ Female Weight: __ __ __ . __ kg Height: __ __ __ cm Date of Birth: __ __ / __ __ __ / __ __ __ __ Age: __ __ years Arm: ☐ 1: Gem ☐ 2: GemCap

Section B: SERIOUS ADVERSE EVENT INFORMATION

Date of Onset: __ __ / __ __ __ / __ __ __ __ Date of Offset (if resolved): __ __ / __ __ __ / __ __ __ __

Outcome: ☐ Resolved ☐ Resolved with sequelae ☐ Not resolved/Ongoing ☐ Ongoing at death ☐ Fatal (i.e. caused death) ☐ Lost to follow-up

Serious Adverse Event Description (signs and symptoms) and Diagnosis (if applicable)	**CTC Grade** If applicable	**Severity** 1 = Mild, 2 = Moderate, 3 = Severe 4 = Life Threatening, 5 = Death
Overall Diagnosis:		

Relevant test results/lab data:

_____

_____

UNANSWERED QUESTIONS MUST BE COMPLETED ON A FOLLOW UP REPORT

PRINCIPAL INVESTIGATOR: PRINT NAME: _____

SIGNED: _____ **DATE:** __ __ / __ __ __ / __ __ __ __

SSES4_D018/6, Date: 11/08/2010

ESPAC-4
European Study Of Adjuvant Chemotherapies In Resectable Pancreatic Cancer
Serious Adverse Event Form (Page 2)

E	S	P	A	C	4

PROJECT

TRIAL NUMBER

PATIENT INITIALS

Section C: CHANGE IN DRUG/TREATMENT

	Yes	No	N/A
Drug/treatment withdrawn	☐	☐	
Drug/treatment reduced	☐	☐	
If withdrawn or reduced did symptoms resolve?	☐	☐	☐
Did event reappear if study drug/treatment reintroduced?	☐	☐	☐

Section D: CAUSALITY

In your opinion was the adverse event related to:	**No**	**Unlikely**	**Possibly**	**Probably**	**Highly Probable**
Study Drug: Gemcitabine	☐	☐	☐	☐	☐
Study Drug: Capecitabine	☐	☐	☐	☐	☐
Subject's original condition / other illness	☐	☐	☐	☐	☐

Section E: SEVERITY

DEFINITION OF 'SERIOUS' - TICK ALL THAT APPLY

☐ Subject died: → Date of Death: __ __ / __ __ __ / __ __ __ __

☐ Involved or prolonged hospitalisation: → Date of admission: __ __ / __ __ __ / __ __ __ __

→ Date of discharge: __ __ / __ __ __ / __ __ __ __

☐ Involved permanent or significant disability or incapacity

☐ Life threatening

☐ Congenital anomaly

☐ Other: please specify: _____

_____

UNANSWERED QUESTIONS MUST BE COMPLETED ON A FOLLOW UP REPORT

PRINCIPAL INVESTIGATOR: PRINT NAME: _____

SIGNED: _____ **DATE:** __ __ / __ __ __ / __ __ __ __

ESPAC-4
European Study Of Adjuvant Chemotherapies In Resectable Pancreatic Cancer
Serious Adverse Event Form (Page 3)

E	S	P	A	C	4

PROJECT

TRIAL NUMBER

PATIENT INITIALS

All follow-up information on drug causality MUST be added to THIS form. Please write in CAPITAL letters.

Section F: TRIAL MEDICATION AND CONCURRENT DRUG INFORMATION

No	Drug	Route (IV, PO, etc)	Dose & Units (or infusion rate, if IV)	Frequency (od, prn, per protocol, etc)	Date (dd/mon/yyyy) Started	Date (dd/mon/yyyy) Stopped If continuing enter 'Cont'	Disease Indication	Is drug suspected of causing SAE?
1	GEMCITABINE	IV			__/___/____	__/___/____	CA PANCREAS	Yes / No
2	CAPECITABINE (if not applicable enter N/A)	PO			__/___/____	__/___/____	CA PANCREAS	Yes / No
3					__/___/____	__/___/____		Yes / No
4					__/___/____	__/___/____		Yes / No
5					__/___/____	__/___/____		Yes / No
6					__/___/____	__/___/____		Yes / No
7					__/___/____	__/___/____		Yes / No
8					__/___/____	__/___/____		Yes / No
9					__/___/____	__/___/____		Yes / No
10					__/___/____	__/___/____		Yes / No

Please fax all 3 completed pages to the Liverpool Cancer Trials Unit on +44 (0) 151 794 8247

UNANSWERED QUESTIONS WILL BE DATA QUERIED BY THE LCTU

PI: PRINT NAME: _____ **SIGNED:** _____ **DATE:** __/__/____

EudraCT Number: 2007-004299-38
Version: 9, Date: 7 January 2014

APPENDIX 12. GP Letter (Version: 2 Date: 21/07/11)

GP Letter

GP Name
GP Address 1
GP Address 2
GP Address 3
GP Post Code

Dear Dr. _____

Re: ESPAC-4. A European Study of Combination versus Single Agent Adjuvant Chemotherapies in Resectable Pancreatic Ductal and Peri-ampullary Cancers

Patient name: _____

Date of Birth: __ __ / __ __ __ / __ __ __ __

NHS Number: __ __ __ __ __ __ __ __ __ __

After giving written informed consent, the above patient has been entered into a clinical trial which will compare combination gemcitabine and capecitabine with gemcitabine alone when used as adjuvant therapy following resection either for pancreatic ductal adenocarcinoma or for peri-ampullary carcinoma.

Your patient has been randomised to receive:

1) Gemcitabine and capecitabine*

2) Gemcitabine

*** Delete as appropriate.**

These chemotherapy agents are associated with side effects such as myelosuppression, gastro-intestinal disturbance, redness and swelling of the hands and/or feet and general tiredness.

As part of the trial, your patient will be required to attend the hospital for approximately 3 out of every 4 weeks to receive gemcitabine (24 week duration). All patients will be followed up in clinic every 3 months until 60 months following randomisation.

If you require further details please contact _____

Yours sincerely,

APPENDIX 13. Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

APPENDIX 14. Summary of Product Characteristics – Gemcitabine

http://www.medicines.org.uk/EMC/searchresults.aspx?term=gemcitabine&searchtype=QuickSearch

APPENDIX 15. Summary of Product Characteristics – Capecitabine

http://www.medicines.org.uk/EMC/searchresults.aspx?term=capecitabine&searchtype=QuickSearch

APPENDIX 16. Registration and Pathology Proforma (V11 Date: 04/04/12)

ESPAC-4

European Study of Combination versus Single Agent Adjuvant Chemotherapies in Resectable Pancreatic Ductal And Peri-Ampullary Cancers

Patient Registration and Pathology Form

Responsible Hospital: _____

Principal Investigator: _____

☐ Oncologist ☐ Surgeon

P.I.'s Telephone Number: _____

Randomising Doctor: _____

☐ **Oncologist** ☐ **Surgeon**

Patient initials: ☐☐☐

Date of Birth: __ __ / __ __ __ / __ __ __ __

Date of Surgery: __ __ / __ __ __ / __ __ __ __

Screening Date: __ __ / __ __ __ / __ __ __ __

Screening Number: ☐☐☐☐☐☐☐

Date of Consent to Trial: __ __ / __ __ __ / __ __ __ __

Sex (circle): Male / Female

Eligibility Criteria

01A. ☐ Histologically proven pancreatic ductal adenocarcinoma (or variant as on page 2 of this form) macroscopically resected (R0 or R1).

OR

01B. ☐ Histologically proven peri-ampullary cancer macroscopically resected (R0 or R1).

01A or 01B
Specify resection margin status:
☐ **R0** ☐ **R1**

02. ☐ No evidence of malignant ascites, liver metastasis, spread to other distant abdominal organs, peritoneal metastasis, spread to extra-abdominal organs.

03. ☐ Contrast-enhanced CT scan of chest, abdomen and pelvis within last 3 months.

04. ☐ No previous or concurrent malignancy diagnoses (except basal cell carcinoma of skin, carcinoma-in-situ of cervix or screen-detected early breast cancer).

05. ☐ No pancreatic lymphoma.

06. ☐ No previous neo-adjuvant chemotherapy or other concomitant chemotherapy.

07. ☐ Patients aged ≥ 18 years.

08. ☐ WHO performance status ≤ 2.

09. ☐ Creatinine clearance ≥ 50ml/min (according to Cockcroft and Gault or equivalent value following local practice).

10. ☐ Reasonably fully recovered from operation, fit to take part in trial with life expectancy >3 months.

11. ☐ Randomisation ideally within 12 weeks post-resection and able to attend for administration of adjuvant therapy within 14 weeks post-resection. **N.B.** Patients beyond 12 weeks may still be considered; contact LCTU for CI approval.

12. ☐ Able to attend for long-term follow-up.

13. ☐ No serious medical or psychological condition precluding adjuvant treatment.

14. ☐ Patient not pregnant.

15. ☐ Patients (both sexes) of reproductive capability must be using a reliable method of contraception.

16. ☐ Fully informed written consent given.

WHO Performance Status: ☐ 0 ☐ 1 ☐ 2 ■ 3 ■ 4

Translational samples taken or to be taken: ☐ Pre-op ☐ Frozen Tissue ☐ PET ☐ Pre-chemo ☐ 3-month

To randomise: fax all 4 pages of this form along with a copy of the patient's written Informed Consent & histology report to the Cancer Research UK Liverpool Cancer Trials Unit office; Fax: 0151 794 8247 (Tel: 0151 794 8932).

****** FOR TRIALS OFFICE ONLY ******

Patient randomised to: _____ Trial Number: ☐☐☐☐☐☐

Randomised by	Checked by	Date
		__ __ / __ __ __ / __ __ __ __

ESPAC-4

European Study of Combination versus Single Agent Adjuvant Chemotherapies in Resectable Pancreatic Ductal And Peri-Ampullary Cancers

Patient Registration and Pathology Form

Screening Number: | | | | | | | | OR Trial Number: | | | | | | |

BIOCHEMISTRY

		CA19.9	CRP	Bilirubin
Pre-op	Result:	_ _ _ _ _ _ _ . _ _ kU/l	_ _ _ _ _ _ _ . _ _ mg/l	_ _ _ _ _ _ _ . _ _ µmol/l
	Date:	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _
Post-op	Result:	_ _ _ _ _ _ _ . _ _ kU/l	_ _ _ _ _ _ _ . _ _ mg/l	_ _ _ _ _ _ _ . _ _ µmol/l
	Date:	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _

HAEMATOLOGY

		Platelets	Lymphocytes
Pre-op	Result:	_ _ _ _ _ _ _ . _ _ x10^9/l	_ _ _ _ _ _ _ . _ _ x10^9/l
	Date:	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _
Post-op	Result:	_ _ _ _ _ _ _ . _ _ x10^9/l	_ _ _ _ _ _ _ . _ _ x10^9/l
	Date:	_ _/_ _ _/_ _ _ _	_ _/_ _ _/_ _ _ _

For all bloods:
Ideally the pre-op values should be as close as possible prior to the operation and the post-op values should be from the first outpatient appointment after surgery.

PATHOLOGY PROFORMA – Histological Information

01A. Tumour Type: **OR** **01B. Tumour Type:**

☐ Pancreatic ductal adenocarcinoma

☐ Variant:

- ☐ Adenosquamous carcinoma
- ☐ Mucinous non-cystic (colloid) carcinoma
- ☐ Signet-ring cell carcinoma
- ☐ Undifferentiated (anaplastic) carcinoma
- ☐ Undifferentiated ca with osteoclast-like giant cells
- ☐ Acinar cell carcinoma
- ☐ Acinar cell cystadenocarcinoma
- ☐ Intraductal papillary-mucinous ca (invasive)
- ☐ Mixed acinar-endocrine carcinoma
- ☐ Mixed ductal-endocrine carcinoma
- ☐ Mucinous cystadenocarcinoma
- ☐ Serous cystadenocarcinoma
- ☐ Solid-pseudopapillary carcinoma
- ☐ Miscellaneous carcinomas: specify:

_____

☐ Peri-ampullary carcinoma: specify:

- ☐ A) Intestinal adenocarcinoma
- ☐ B) Pancreatobiliary adenocarcinoma
- ☐ C) Mixed Intestinal/Pancreatobiliary
- ☐ D) Indeterminate (i.e. not sure if it is A, B or C)
- ☐ E) Other carcinomas: specify:

_____

Tumour Location:

- ☐ i) Pancreas (ICD-O C25)
- ☐ ii) Ampulla of Vater (ICD-O C24.1)
- ☐ iii) Extrahepatic bile ducts - distal (ICD-O C24.0)
- ☐ iv) Small intestine (ICD-O C17)
- ☐ v) Other: _____

Maximum Tumour Dimension: _ _ _ mm

Differentiation: ☐ Well ☐ Well-Moderate ☐ Moderate ☐ Moderate-Poor ☐ Poor ☐ Undifferentiated

ESPAC-4

European Study of Combination versus Single Agent Adjuvant Chemotherapies in Resectable Pancreatic Ductal And Peri-Ampullary Cancers

Patient Registration and Pathology Form

Screening Number: | | | | | | | | OR Trial Number: | | | | | | |

LYMPH NODES

Total number: __ __ Number positive: __ __

Locations	Lymph nodes present?	Number positive	Out of
Anterior pancreatoduodenal (17a, b)	☐Not reported ☐No ☐Yes:	__ __	__ __
Posterior pancreatoduodenal (13a, b)	☐Not reported ☐No ☐Yes:	__ __	__ __
Hepatoduodenal (12b1, b2, c)	☐Not reported ☐No ☐Yes:	__ __	__ __
Superior mesenteric (14a, b)	☐Not reported ☐No ☐Yes:	__ __	__ __
Infrapyloric (6)	☐Not reported ☐No ☐Yes:	__ __	__ __
Common hepatic artery (8a)	☐Not reported ☐No ☐Yes:	__ __	__ __
Retroperitoneal (16b1)	☐Not reported ☐No ☐Yes:	__ __	__ __
Other: _____	☐Not reported ☐No ☐Yes:	__ __	__ __

RESECTION MARGINS: for ESPAC-4 a positive margin is defined as within 1mm of the resection margin.

Resection margin	Involved?	Directly?	Positive lymph node at margin?
Posterior	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
Anterior	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
SMV groove	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
Pancreatic neck	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
Bile duct	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
Duodenal resection	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
or			
Gastric resection	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No
Other: _____	☐Not reported ☐No ☐Yes:	☐Yes ☐No	☐Yes ☐No

If the information for the above tables is not stated in the histology report just tick 'Not reported'.

Named vessel involvement

☐ No
☐ Not assessed
☐ Yes:
- ☐ Portal vein
- ☐ Superior mesenteric vein
- ☐ Superior mesenteric artery
- ☐ Other: _____

Perineural invasion ☐ Yes ☐ No ☐ Not assessed

ESPAC-4

European Study of Combination versus Single Agent Adjuvant Chemotherapies in Resectable Pancreatic Ductal And Peri-Ampullary Cancers

Patient Registration and Pathology Form

Screening Number: | | | | | | | | **OR** Trial Number: | | | | | | |

TNM Stage (UICC, 7th Edition, 2009)

Tumour:

For all tumours: ☐ pT1 ☐ pT2 ☐ pT3 ☐ pT4

Nodes:

For tumours of the pancreas, ampulla of Vater and extrahepatic bile ducts - distal: ☐ pN0 ☐ pN1

For tumours of the peri-ampullary duodenum: ☐ pN0 ☐ pN1 ☐ pN2

Metastases:

For all tumours: ☐ Mx ☐ M0 ■ M1

Assessed clinically / radiologically

R Status (N.B. For ESPAC-4 a positive margin is defined as within 1mm of ANY margin)

☐ R0 ☐ R1 ■ R2

Stage Grouping

For tumours of the pancreas, ampulla of Vater and extrahepatic bile ducts - distal:

☐ Ia ☐ Ib ☐ IIa ☐ IIb ☐ III ■ IV

For tumours of the peri-ampullary duodenum:

☐ I ☐ IIa ☐ IIb ☐ IIIa ☐ IIIb ■ IV

Surgery sample histology / laboratory number: _____

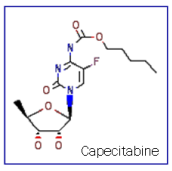
UNANSWERED QUESTIONS WILL BE DATA QUERIED BY THE LCTU

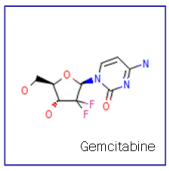
SIGNED: _____ **DATE:** __ __ / __ __ __ / __ __ __ __

APPENDIX 17. ESPAC-4 Information Leaflet (Version: 7 Date: 04/04/12)

ESPAC-4 Trial

The study is a two arm, open-label, phase III, multi-centre, randomised, controlled trial.



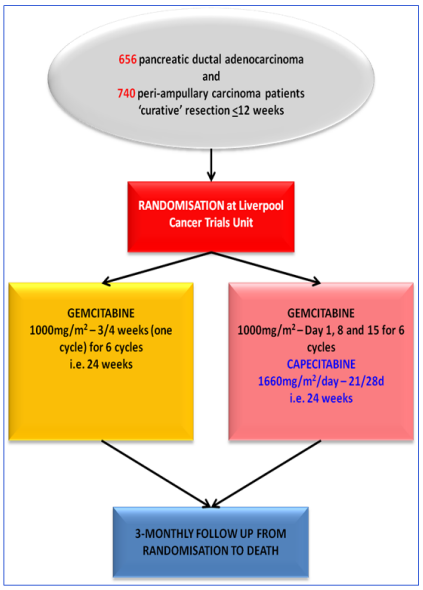


The aim of this trial is to compare survival following resection and either adjuvant **gemcitabine plus capecitabine** or **gemcitabine alone** in patients either with pancreatic ductal or peri-ampullary carcinomas.

Treatment

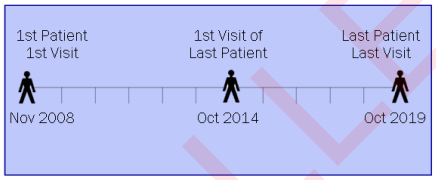
Arm 1 – Gemcitabine alone
Gemcitabine 1000mg/m^2 is given as an i.v. infusion over 30 minutes, the lyophilized powder being diluted in normal saline, will be administered once a week for three weeks out of every four weeks (one cycle) for six cycles i.e. 24 weeks.

Arm 2 – Gemcitabine and Capecitabine Therapy
Gemcitabine 1000mg/m^2 is given as an i.v. infusion over 30 minutes, the lyophilized powder being diluted in normal saline. This will be administered on day 1, 8 and 15. Capecitabine 1660mg/m^2/day in two divided doses administered orally for 21 days followed by 7 days' rest. Treatment will be repeated every 4 weeks for a total of 24 weeks.



Time Schedule

Planned recruitment/finish dates for the trial



Statistical Considerations

Patients with resected pancreatic ductal adeno-carcinoma and peri-ampullary carcinomas will be randomised between the two arms.

656 ductal patients will permit 90% power and 740 peri-ampullary patients will permit 80% power to detect at least a 10% absolute improvement in survival rate at 2 and 4 years, respectively, in the combination group.

The primary outcome measure is overall survival from randomisation.

The secondary outcome measures are:

1. Toxicity
2. Quality of Life
3. Survival rate at 2 (ductal) / 4 (periamp) years
4. Survival rates at 5 years (ductal only)
5. Relapse free survival

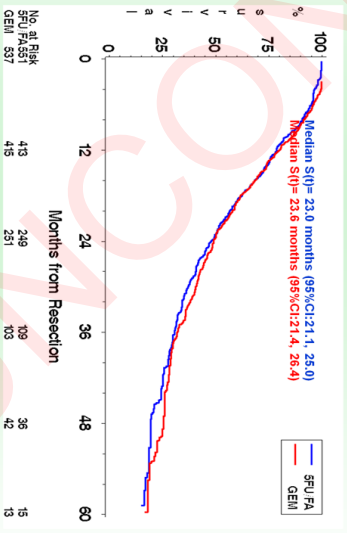
Planned close date	31/10/2014
Target number of patients	1396
Number of centres open	**79**
Total recruitment to date	**344**
Recruitment: UK	247
Recruitment: Sweden	52
Recruitment: Germany	24
Recruitment: France	24

As of 04/04/2012

ESPAC-4 recruited its first patient in November 2008. Current recruitment stands at 344 ductal patients. Peri-ampullary tumour patients have now been added with an accrual target of 740.

ESPAC-3 opened in July 2000 and recruited 1583 patients in 159 centres across 19 countries and is the largest adjuvant trial ever conducted for pancreatic ductal adeno-carcinoma.

The two year survival analysis of the ductal patients was presented at ASCO 2009 and showed no significant difference in survival between adjuvant 5FU/FA and adjuvant GEM. The two year peri-ampullary analysis is due soon.



The LCTU

The Liverpool Cancer Trials Unit works closely with Cancer Research UK in the clinical research of new and existing products for the treatment of cancer, easing suffering and improving the quality of life for cancer patients.

Further Information

Trial Co-ordinator: Karl Harvey
karl.harvey@liverpool.ac.uk
Trial Monitor: David King
d.king@liverpool.ac.uk
Data Manager: Ron Wall
wallr@liverpool.ac.uk

For more information about pancreatic cancer or current trials running within the Liverpool Cancer Trials Unit, please email: lctu@liverpool.ac.uk

Or visit the ESPAC-4 website:

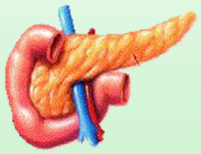
www.lctu.org.uk/espac4

LCTU

ESPAC-4 Leaflet Version: 7 Date: 04/04/2012

LCTU Liverpool Cancer Trials Unit

ESPAC-4



EUROPEAN STUDY GROUP FOR PANCREATIC CANCER - TRIAL 4.

Combination versus single agent chemotherapy in resectable pancreatic ductal and peri-ampullary cancers

EudraCT No.: 2007-004299-38

ISRCTN No.: ISRCTN96397434