EUROPEAN STUDY GROUP FOR PANCREATIC CANCER
TRIAL 5F

Four arm, prospective, multicentre, randomised, feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy.

National Cancer Research Institute (NCRI)

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EudraCT number: 2013-003932-56
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Protocol version: 6
Date: 27.01.2017
Study Protocol Approval

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General Information

This document describes the ESPAC-5F trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Cancer Trials Unit (LCTU)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via LCTU.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTU Standard Operating Procedures and 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

UK Registration

This study will have National Research Ethics Service (NRES) approval and hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). Each centre must also undergo Site Specific Assessment by the relevant Trust Research and Development department (or Local Research Ethics Committee for Non-NHS Sites) and NHS sites must be granted Research and Development Approval from each Trust where the trial will be carried out.
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<td>LCTU Core Trial Monitor</td>
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<td>International Conference on Harmonisation</td>
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<td>Investigational Medicinal Product</td>
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<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
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<td>Independent Ethics Committee</td>
<td>TSC</td>
<td>Trial Steering Committee</td>
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<td>INR</td>
<td>International Normalized Ratio</td>
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<td>Unexpected Adverse Reaction</td>
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<td>IRAS</td>
<td>Integrated Research Applications System</td>
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<td>Upper Limit of Normal</td>
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1 PROTOCOL SUMMARY

Title: ESPAC-5F. Four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy for patients with borderline resectable adenocarcinoma of the pancreas.

Phase: Feasibility Phase II.
Sample Size: 100 patients. UK and Europe.

Main Inclusion Criteria:
1. Borderline resectable mass in the pancreatic head as defined by CT criteria (see Table 1).
2. Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants).
3. Able to undergo biliary drainage using a covered, partially covered or uncovered self-expanding metal stent.
4. Age ≥ 18 years.
5. WHO performance status 0, 1.
6. Platelets >100 x 10^9/l; WBC > 3 x 10^9/l; neutrophils > 1.5 x 10^9/l.
7. Serum bilirubin <1.5 ULN.
8. Glomerular filtration rate estimated >50ml/min according to Cockcroft & Gault (or equivalent value following local scale/formula).
9. Able to comply with protocol requirements and deemed fit for surgical resection, chemotherapy and radiotherapy.
10. Written informed consent.

Main Exclusion Criteria:
1. Distant metastatic disease.
2. Previous or concurrent malignancy diagnoses, except curatively-treated (i) basal cell carcinoma of skin, ii) carcinoma in situ of cervix; breast; bladder; (iii) non muscle invasive transitional cell carcinoma of the bladder; iv) previous cancers treated with curative intent, ending treatment ≥ 3 years ago.
3. Serious medical or psychological condition precluding neoadjuvant treatment and surgical resection.
4. Previous chemotherapy ending < 3 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis).
5. Pregnancy.
6. WHO status 2-4.
7. New York Heart Association Classification Grade III or IV.
8. Uncontrolled angina/ischaemic heart disease.
9. Patients with known malabsorption.
No. of Sites: Up to 24 sites, 21 in the UK and 3 sites in Europe.

Study Duration: 12 months per patient.

Description of Agent / Intervention:

Arm A (40 patients) (control): Surgery

Eligible patients will undergo surgical exploration for resection within two weeks of randomisation.

Arm B (20 patients): GEMCAP

Within two weeks of randomisation, eligible patients will commence neoadjuvant gemcitabine, 1000mg/m² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle and capecitabine 830mg/m² BD PO for 21 out of 28 days (one cycle) for 2 cycles i.e. 8 weeks.

Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A.

Arm C (20 patients): FOLFIRINOX

Within two weeks of randomisation, eligible patients will commence neoadjuvant oxaliplatin 85mg/m², irinotecan 180mg/m², folinic acid given according to local practice for both the drug and the dose, 5-FU 400mg/m² bolus injection followed by 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles i.e. 8 weeks. Growth factor support may be administered at the investigator’s discretion.

Four to six weeks after completion of chemotherapy patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A.

Arm D (20 patients): Chemoradiotherapy

Within two weeks of randomisation, eligible patients will commence neoadjuvant chemoradiotherapy (CRT) delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/fraction, Mon to Fri) with capecitabine 830mg/m² BD PO (Mon to Fri) throughout radiotherapy.

Four to six weeks after completion of CRT patients will undergo a staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as in Arm A.

All patients (arms A-D)

Following recovery from successful resection (up to 12 weeks) patients will undergo standard adjuvant treatment as per physician’s choice.

If patients do not undergo successful resection then following recovery from surgery, further therapy will be as physician’s choice.

All patients will be followed up for 12 months after randomisation.
Objectives: Primary:

1. Recruitment rate: Recruitment will be measured by (i) recruitment rate by centre (ii) overall recruitment rate and (iii) graph comparing expected versus actual cumulative recruitment.

2. Resection rate (R1 + R0): Resection rate will be measured using the total number of patients in the arm as baseline and, secondly, using the number of patients having explorative surgery. R1 and R0 resection margins will be included in the resection rate but not R2 resection. R1 will be defined as per the Royal College of Pathologists (RCP) report on Standards and datasets for reporting cancers [47].

Secondary:

1. R0 resection margin rate: R0 resection rate will be recorded according to the RCP report on Standards and datasets for reporting cancers [47].

2. Toxicity: Toxicity will be graded according to the NCI-CTCAE v4.

3. Post-operative complication rate: Post-operative morbidity will be recorded following surgery and classified according to existing guidelines.

4. Post-operative mortality rate: Post-operative mortality rate will be recorded as the 30 day mortality rate.

5. Response rate: Response rate will be recorded according to RECIST 1.1 criteria.[41] www.recist.com/files/Recist-1.1-Fanbook.pdf

6. Disease free survival rate: DFS will be defined as number of days between date of surgery and disease recurrence (CT scan, +/- clinical assessment +/- CA19.9).

7. Local disease free survival rate: Local DFS will be defined as number of days between date of surgery and local disease recurrence (CT scan).

8. Overall survival: OS will be defined as the 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).

9. Quality of life: QoL forms (EORTC QLQ-C30 version 3) will be completed as per the Table of Assessments in Section 8
Protocol Summary – continued

Schematic of Study Design:

- Eligible patients with borderline resectable pancreatic cancer. Fit for surgery, chemotherapy and chemoradiotherapy. Multi-detector CT scan (MDCT), ERCP (metal stent) + brushings and or EUS + FNA, CA19.9 +/- selective laparoscopy

  Informed written consent (Main Trial/Translational Study)

  Randomise:
  stratification by centre

  - Arm A (40 patients)
    - SURGERY: Resection
      - No
        -> Palliative therapy
      - Yes
        -> Gemcitabine, 1000mg/m² iv infusion over 30 minutes, D1, 8, 15 of a 28 day cycle
        -> Captopril, 850mg/m² BD PO for 21/28 days (one cycle) for 2 cycles
    - Palliative therapy

  - Arm B (20 patients)
    - GEMCAP
    - Palliative therapy

  - Arm C (20 patients)
    - FOLIRINOX
    - Palliative therapy

  - Arm D (20 patients)
    - CHEMORADIOThERAPY
      - CRT delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/#, Mon – Fri) with Captopril, 830mg/m² BD PO (Mon – Fri) throughout Radiotherapy

  Re-staging CT at 4-6 weeks

  - Tumour still borderline resectable? (No disease progression)
    - Yes
      -> SURGERY: resection
    - No
      -> Palliative therapy

  - Palliative therapy

  Adjuvant treatment: as per physicians choice

All patients followed up for 12 months after randomisation
2 BACKGROUND INFORMATION

2.1 Introduction

Patients with borderline resectable pancreatic cancer (BR) have low resection rates and poor survival compared with patients who have clearly resectable (RS) tumours despite high quality surgery and adjuvant therapy. The addition of neoadjuvant therapy needs to be assessed in this group of patients to see if their outcomes can be improved.

In the UK there were 8,085 patients with pancreatic cancer with 7,781 cancer deaths in 2008 [1]. At presentation, approximately 10-20% of patients have RS, 30-40% locally advanced disease (LA) and 50-60% metastatic disease [2]. Most studies group BR with LA patients, the best estimates from published data [3-5] and our own study suggest the BR population approximates to 5-10% of all patients presenting with pancreatic cancer.

The track record from previous and ongoing trials in the UK would suggest that a high proportion of eligible patients would enter clinical trials. Neoadjuvant therapy is not a standard of care in this disease and internationally randomised studies of neo-adjuvant therapy versus surgery have closed early due to poor recruitment [6,7]. A feasibility study is therefore required.

2.2 Rationale

There is a growing international momentum to assess the role of neoadjuvant therapy in pancreatic cancer. This potentially represents a significant shift in the approach to the management of pancreatic cancer and is reflected in rising numbers of registered randomised trials which are being proposed [8-10]. Following resection, patients benefit from the use of adjuvant chemotherapy [11-13] but there is still room for improvement. A large meta-analysis [14] of neoadjuvant therapy found that patients with initially unresectable disease (BR/LA) benefited the most from neoadjuvant therapy with an overall response rate of 35%. The outcome in this group of patients treated was comparable to patients with clearly resectable disease [23.3 mo v 20.5 mo]. There is overwhelming enthusiasm and support for a trial to look at the use of neoadjuvant therapy in this group of patients both nationally and internationally and it is vital that we take this opportunity to do so now. A clear definition of BR pancreatic cancer is required. For this study, a consensus has been reached with UK pancreatic surgeons (Pancreatic Society of Great Britain and Ireland and AUGIS members) and ESPAC colleagues (see Table 1) modified from published criteria [4, 16-20].

In the UK, patients with BR tumours undergo attempted pancreatic resection as part of standard clinical practice. Despite optimum therapy including adjuvant chemotherapy, patients with borderline resectable disease have low resection rates, high R1 margin rates and poor survival [18,19,21]. In a pilot study in our centre (to be submitted) we looked at 366 patients who had surgery for PDAC, of which 276 were deemed RS and 90 BR. The resection rate was significantly lower for the BR group (40% vs. 88%, p=<0.001), as was overall survival 6.3 months (95% CI 4.7-8.0) vs. 14.5 months (95% CI 12.8-16.2), p=<0.001). Median survival for BR patients undergoing successful resection compared to the RS group was 10.9 months vs. 15.1 months, (p=0.096) respectively.
Table 1. Definition of borderline resectable pancreatic cancer (modified from [4, 16-20])

<table>
<thead>
<tr>
<th>Features</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable (RS)</td>
<td></td>
</tr>
<tr>
<td>a. Normal tissue plane between tumour and vessels.</td>
<td>a and b</td>
</tr>
<tr>
<td>b. No evidence of metastatic disease.</td>
<td></td>
</tr>
<tr>
<td>Borderline resectable (BR)</td>
<td></td>
</tr>
<tr>
<td>a. Loss of normal tissue plane between tumour and vessels.</td>
<td>a and or b and /or c plus d</td>
</tr>
<tr>
<td>b. Venous involvement (contact and or distortion) of the SMV, PV or SMV-PV confluence – allowing surgical reconstruction.</td>
<td></td>
</tr>
<tr>
<td>c. Tumour abutment &lt;180° of the SMA or coeliac axis.</td>
<td></td>
</tr>
<tr>
<td>d. No evidence of metastatic disease.</td>
<td></td>
</tr>
<tr>
<td>Unresectable</td>
<td></td>
</tr>
<tr>
<td>a. Encasement/contact of SMA or coeliac axis of &gt;180°.</td>
<td>one or more of a, b, c, d</td>
</tr>
<tr>
<td>b. Long segment involvement/occlusion of the SMV, PV or SMV-PV confluence with no reconstruction possible.</td>
<td></td>
</tr>
<tr>
<td>c. Encasement of the hepatic artery.</td>
<td></td>
</tr>
<tr>
<td>d. Confirmed metastatic disease.</td>
<td></td>
</tr>
</tbody>
</table>

SMA = superior mesenteric artery; SMV = superior mesenteric vein; PV = portal vein.

The aim of this study is to compare immediate surgery (Arm A) with neoadjuvant chemotherapies (Arms B and C) or chemoradiotherapy (CRT) (Arm D) and follow on surgery in patients with BR pancreatic cancer. The addition of neoadjuvant therapy may increase the proportion of patients who can be resected and treat micro metastatic disease at an earlier stage and this may translate into a survival benefit [14,15]. There are a proportion of patients that develop early metastatic disease following resection [22]. Neoadjuvant therapy would allow us to identify this group of patients where surgical therapy would have been inappropriate. There is also the opportunity to collect samples pre and post neoadjuvant therapy to allow for predictive biomarker studies. Currently there is no clear evidence to indicate if either neoadjuvant chemotherapy (CT) or chemoradiotherapy (CRT) is superior [14,15,23-26]. At this stage a randomized neoadjuvant trial should include both CT and CRT arms to evaluate the relative merits/demerits of either modality. The proposed CT and CRT arms have demonstrated the best survival and response rates in Phase III trials +/- meta-analyses.

**Arm A: Immediate surgery:** Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy. Total pancreatectomy will be accepted if clinically indicated (for details see section 17 of the Surgical Handbook, SSESSF_D031).

**Arm B: Gemcitabine plus capecitabine (GEMCAP):** GEMCAP versus gemcitabine demonstrated significantly improved objective response rate (19.1% v 12.4%; P = .034) and progression-free survival (hazard ratio [HR], 0.78; 95% CI, 0.66 to 0.93; P = .004) in patients with advanced pancreatic cancer [27]. 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 to 0.98; P = .02) versus gemcitabine [27]. Neoadjuvant GEMCAP has been used in forty-three patients (18 with BR disease and 25 with LA disease). The radiologic response rate was 18.6%, median overall survival was 23.1 months in patients who underwent surgery and 13.2 months in patients unable to complete surgery (P = .017) [28].

**Arm C: Oxaliplatin, irinotecan, fluorouracil, and Folinic acid (FOLFIRINOX):** A Phase III trial of patients with metastatic pancreatic cancer comparing FOLFIRINOX with gemcitabine; demonstrated median overall survival of 11.1 months with FOLFIRINOX versus 6.8 months with gemcitabine (HR, 0.57; 95% [CI], 0.45 to 0.73; P<0.001). Median progression-free survival was 6.4 months with FOLFIRINOX versus 3.3 months with gemcitabine (HR, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate was 31.6% with FOLFIRINOX versus 9.4% with gemcitabine (P<0.001) [29]. The majority of patients in this trial had body and tail tumours and good performance status. This has implications for ESPAC 5 in terms of toxicity, as patients will have pancreatic head tumours causing obstructive jaundice. All patients will have adequate biliary drainage prior to treatment.
study of neoadjuvant FOLFIRINOX in 18 patients with LA or BR has been published [30]. Eleven (61%) patients had pancreatic head tumours. 7 (39%) were converted to resectability by radiological criteria. 1-year progression-free and overall survival was 83% (95% CI 59-96%) and 100% (95% CI 85-100%) respectively.

**Arm D: Capecitabine based chemoradiotherapy (CRT):** Chemoradiotherapy [CRT] has been the commonest modality tested in neoadjuvant therapy [14,15]. The only phase III study of neo-adjuvant therapy in patients with resectable pancreatic cancer, closed early due to poor recruitment (personal communication T Brunner). 73 patients were randomised between immediate surgery [n=37] versus a neoadjuvant CRT [n=36] consisting of combination gemcitabine/cisplatin chemotherapy and 55Gy radiation. In the neo-adjuvant group, 20/36 patients underwent curative resection. The R0 resection rate [90% v 67%] and isolated local recurrence rate [10% v 25%] favoured neo-adjuvant therapy. There was a trend towards overall survival benefit [25 mo v 18 mo] which did not reach statistical significance. The choice of CRT for this study is fluoropyrimidine [capecitabine] based CRT which has been widely used [31,32] and draws on UK experience (SCALOP I). 50.4 Gy in 28 fractions was used in the SCALOP I trial with no significant concerns regarding toxicity. Therefore the same dose – fractionation has been proposed for this trial.

This is a feasibility trial with feasibility endpoints. There are many challenges to be addressed which include: recruitment of these patients to a randomised multi-arm neoadjuvant trial; toxicity associated with neoadjuvant therapy (particularly FOLFIRINOX in pancreatic head tumours); setting the standards and quality control for surgery across sites; establishing centralised reporting for all CT scans; ensuring high level radiotherapy QA across sites; feasibility of sample collection. Actions to address this issues: The success of previous (ESPAC-1, 3v2 [11,12]) and ongoing (ESPAC-4, ESPAC-4T) ESPAC trials provide the infrastructure and collaboration needed for a neoadjuvant study in pancreatic cancer, ensuring excellent study oversight and safety reporting. A surgical working party has been established to set minimum standards for surgery and quality control. All PIs will attend surgical workshops. Central review of radiology will be undertaken. A standard template will be used for reporting. A radiotherapy working party has been established to ensure that the best radiotherapy will be delivered for this study. The SCALOP trial [CI S Mukherjee] has demonstrated the feasibility of delivering CRT safely across multiple centres in the UK. ESPAC 5 will draw on the experience and the radiation expertise from the SCALOP team and the radiotherapy protocol and quality assurance will be developed in close collaboration with the recently funded SCALOP II trial. The aims will be to continue to develop a network of regional RT experts and optimise pathways for these studies. The ESPAC 5 protocol has been developed with the input of the NCRI upper GI patient representative and the Chair and members of the CR-UK LCTU PPI steering committee and Chair Royal Liverpool University Hospital Patient’s Council. Develop transferable, adaptive, robust sample collection protocols.

### 2.3 Objectives

The purpose of ESPAC-5F trial is to answer the following research questions:

1. Is it feasible to recruit and randomise patients with borderline resectable pancreatic cancer to receive immediate surgical exploration versus neoadjuvant chemotherapies or chemoradiotherapy?

2. What are the resection rates, resection margin rates, operative morbidity and mortality rates, response rates, toxicity, survival and quality of life associated with neoadjuvant therapies versus immediate surgery?

3. Can we use and include these data in a follow-on Phase III trial to compare survival between neoadjuvant therapies and immediate surgery?

4. Can we identify what type(s) of neoadjuvant therapy should be assessed in a follow-on Phase III trial?

The interventions for each arm are:

Eligible patients will undergo surgical exploration for resection within two weeks of randomisation. Following recovery from successful resection (up to 12 weeks) patients will undergo standard adjuvant treatment as per physician’s choice.

If patients do not undergo successful resection then following recovery from surgery, further therapy will be as physician’s choice. Patients will be followed up for 12 months after randomisation.

Arm B: GEMCAP.

Within two weeks of randomisation, eligible patients will commence neoadjuvant Gemcitabine, 1000mg/m² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 day cycle and capecitabine 830mg/m² BD PO for 21 out of 28 day (one cycle) for 2 cycles, i.e. 8 weeks.

Four to six weeks after completion of neoadjuvant chemotherapy, patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as for Arm A.

Arm C: FOLFIRINOX

Within two weeks of randomisation, eligible patients will commence neoadjuvant Oxaliplatin 85mg/m², Irinotecan 180mg/m², Folinic acid given as per local practice for both the drug and the dose, 5-FU 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles. Growth factor support may be administered at the investigator’s discretion.

Four to six weeks after completion of neoadjuvant chemotherapy, patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as for Arm A.

Arm D: CRT.

Within two weeks of randomisation, eligible patients will commence neoadjuvant CRT delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/#fraction Mon to Fri) with Capecitabine 830mg/m² BD PO (Mon to Fri) throughout radiotherapy. Centres would be required to choose to use IMRT (preferred) or 3D conformal RT for all their patients.

Four to six weeks after completion of chemoradiotherapy, patients will undergo staging CT scan. If there has been no progression patients will then undergo surgical exploration within two weeks as for Arm A.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Surgery

Immediate surgery is standard practice [33,34] and the risks to the patient are as expected for that treatment. Mortality rate is < 5% in specialist centres. The overall complication rate even in specialist centres is 18-54%. Reviews of large series of pancreatic resections shows an incidence of common complications of 10.4% for fistula, 9.9% for delayed gastric emptying, 4.8% for bleeding, 4.8% for wound infection and 3.8% for intra-abdominal abscess [35]. The median hospital stay is 13-18 days in different series. The re-operation rate varies from 4 to 9% with a mortality rate of 23 to 67% [35]. Major complications are a significant factor in post-operative mortality, especially if they require re-operation [36-38]. The use of octreotide or somatostatin to prevent complications is supported by several multicentre, double-blind, randomized controlled trials. The best way to improve outcome is to concentrate pancreatic cancer care in regional specialist centres.
Gemcitabine and Capecitabine

Gemcitabine has a well described toxicity profile when used within the terms of its marketing authorisation. The toxicity profile of gemcitabine in combination with capecitabine as prescribed in this study has been described in a Phase III randomised controlled trial [27].

Folinic acid, 5-Fluorouracil, Oxaliplatin and Irinotecan

Folinic acid has a well described toxicity profile when used within the terms of its marketing authorisation. A recent randomised controlled trial described the toxicity profile when used in combination with Irinotecan, 5-Fluorouracil and Oxaliplatin [29] as prescribed for this study.

Radiotherapy

The risks of upper abdominal radiotherapy are significant because of the proximity of gross tumour volume (GTV) to several critical structures. The optimum balance between efficacy and toxicity will be achieved by employing strict protocol defined target definition and strict CRT QA and will be carefully documented.

2.4.2 Known Potential Benefits

The benefits of different approaches to neoadjuvant therapy have been evaluated in several reviews. There have been four systematic reviews of neoadjuvant therapy in resectable (RS) and BR/LA pancreatic cancer. Gillen et al [14] evaluated 4,394 patients (1443 RS and 1871 BR/LA) in 111 studies. Neoadjuvant chemotherapy was given in 96.4% of the studies with the main agents being GEM and 5FU. Neoadjuvant radiotherapy was applied in 93% of studies with doses from 24 to 63 Gy. In RS tumours, resectability was estimated to 73.6% (95% CI 65.9–80.6%) compared to 33.2% (95% CI 25.8–41.1%) in BR/LA tumours. Estimated median survival following resection was 23.3 (range 12–54) months for RS and 20.5 (range 9–62) months for BR/LA. The complete and partial response rate following neoadjuvant therapy in BR/LA patients was 35% and resection rate was 33%. Neoadjuvant combination chemotherapy had a complete and partial response rate of 40% in this patient group. Assifi et al [15] looked at 536 patients (402 RS and 130 BR/LA) in 14 studies. For the LA/BR patients the complete and partial response rate following neoadjuvant therapy was 32% and resection rate was 31%. Laurence et al [39] looked at neoadjuvant radiotherapy in 19 studies 2148 patients (188 RS and 713 BR/LA) and observed a resection rate following neoadjuvant RT of 40%. Andriulli et al [40] assessed neoadjuvant gemcitabine regimens in 707 patients in 20 studies (345 RS and 362 BR/LA). The complete and partial response rate following neoadjuvant therapy was 27% and resection was 39% in BR/LA patients. They concluded that the BR patients represented 30% of the combined BR/LA group based on response and resection rates. These meta-analyses identified that the BR groups of patients would be the most likely to benefit from neoadjuvant therapy (in terms of response and resection rates) and that a randomised trial is now required. A clear and widely acceptable definition of borderline resectability is also required.

Both GEMCAP and FOLFIRINOX have been shown to increase survival in patients with advanced pancreatic cancer [27,29]. The role of radiotherapy remains to be proven in a Phase III trial, there may be some benefit in this group of patients in a neoadjuvant setting [14] and therefore a randomised trial is required to evaluate this.
3 SELECTION OF CENTRES/CLINICIANS

Each participating centre (and investigator) has been identified on the basis of:

a. Having a surgeon, medical oncologist and clinical oncologist with experience of treating patients with pancreatic cancer in a specialist centre.
b. Showing enthusiasm to participate in the study
c. Ensuring that sufficient time, staff and adequate facilities are available for the trial.
d. Providing information to all supporting staff members involved with the trial or with other elements of the patient's management.
e. Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP) and other regulatory documentation
f. Suitable MDT meeting structure to identify patients and ensure the pathologists and surgeons are involved in patient screening to ensure the required samples are made available for the associated biomarker studies.
g. Surgeons able to participate in surgical workshops.
h. Clinical oncologists able to participate in radiotherapy workshops.
i. Centres able to deliver IMRT or 3D conformal radiotherapy.
j. Able to screen at least 5-10 eligible patients per year.
k. Able to transfer CT images to the central core laboratory.
l. Able to carry out ERCP, PTC, EUS.
m. Able to complete green light process in a timely manner.

3.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) by Local Research and Development (R&D) approval
b. Signed Research Site Agreement including material transfer clauses
c. Receipt of evidence of completion of (a) & (b) by LCTU
d. Completion and return of “Signature and Delegation Log” to LCTU
e. Curriculum Vitae (CV) including a record of GCP training – Principal Investigator (PI)
f. CV including a record of GCP training – Other personnel on the delegation log
g. Clinical Study Protocol Receipt Form
h. Investigator Brochures Receipt Form
i. Local laboratory accreditation/Quality Check
j. Completion of pharmacy practice form
k. Completion of test SAE reported via web
l. Completion of translational study questionnaire
m. Local laboratory reference ranges
n. Patient information sheet, consent form and GP letter on trust headed paper

3.2 Centre/Clinician Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.
4 TRIAL DESIGN

4.1 Overall Design

Four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy. Trial population will be patients with borderline resectable pancreatic cancer. Central randomisation using a computer programme will be undertaken by the CR-UK Liverpool Cancer Trials Unit. There will be allocation concealment. The trial is openlabelled due to the different treatment modalities. Stratification will be by centre. There will be:

40 patients recruited to Arm A (immediate surgery);

20 patients recruited to Arm B (gemcitabine, 1000mg/m² iv infusion over 30 minutes, days 1, 8 and 15 of a 28 days cycle plus capecitabine 830mg/m² BD PO for 21 out of 28 days (one cycle) for 2 cycles for a total of 8 weeks);

20 patients recruited to Arm C (Oxaliplatin 85mg/m², Irinotecan 180mg/m², Folinic acid given as per local practice for both the drug and dose, 5-FU 400mg/m² bolus injection followed by 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles for a total of 8 weeks);

20 patients recruited to Arm D (CRT delivering a total dose of 50.4Gy in 28 daily fractions over 5 1/2 weeks (1.8Gy/# Mon – Fri) with Capecitabine 830mg/m² BD PO (Mon – Fri) throughout radiotherapy).

4.2 Primary Endpoint

1. Recruitment rate.

Recruitment will be measured by:

(i) recruitment rate by centre
(ii) overall recruitment rate
(iii) graph comparing expected versus actual cumulative recruitment.

2. Resection rate (R1 + R0).

Resection rate will be measured using the total number of patients in the arm as baseline and, secondly, using the number of patients having explorative surgery. R1 and R0 resection margins will be included in the resection rate but not R2 resection.

4.3 Secondary Endpoint(s)

1. R0 resection margin rate.

R0 resection rate will be recorded according to the RCP report on Standards and datasets for reporting cancers [47].

2. Toxicity.

Toxicity will be graded according to the NCI-CTCAE v4.

3. Post-operative complication rate.

Post-operative morbidity will be recorded following surgery and classified according to ISGPS guidelines.
4. Post-operative mortality rate.

Post-operative mortality rate will be recorded as the 30 day mortality rate.

5. Response rate.

Response rate will be recorded according to RECIST 1.1 criteria [41] www.recist.com/files/Recist-1.1-Fanbook.pdf.

6. Disease free survival rate.

DFS will be defined as number of days between date of surgery and disease recurrence (CT scan, +/- clinical assessment +/- CA19.9).

7. Local disease free survival rate.

Local DFS will be defined as number of days between date of surgery and local disease recurrence (CT scan).

8. Overall survival.

OS will be defined as the 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).

9. Quality of life.

QoL forms (EORTC QLQ-C30 version 3) [42] will be completed as per the Table of Assessments in Section 8.
5 STUDY POPULATION

Main Inclusion Criteria:

1. Borderline resectable mass in the pancreatic head as defined by CT criteria (see Table 1).
2. Histologically or cytologically proven pancreatic ductal adenocarcinoma (including variants).
3. Able to undergo biliary drainage using a covered, partially covered or uncovered self-expanding metal stent.
4. Age ≥ 18 years.
5. WHO performance status 0, 1.
6. Platelets >100 x 10^9/l; WBC > 3 x 10^9/l; neutrophils > 1.5 x 10^9/l.
7. Serum bilirubin <1.5 ULN.
8. Glomerular filtration rate estimated >50ml/min according to Cockcroft & Gault (or equivalent value following local scale/formula).
9. Able to comply with protocol requirements and deemed fit for surgical resection, chemotherapy and radiotherapy.
10. Written informed consent.

Main Exclusion Criteria:

1. Distant metastatic disease.
2. Previous or concurrent malignancy diagnoses, except curatively-treated (i) basal cell carcinoma of skin, ii) carcinoma in situ of cervix; breast; bladder; (iii) non muscle invasive transitional cell carcinoma of the bladder; iv) previous cancers treated with curative intent, ending treatment ≥ 3 years ago.
3. Serious medical or psychological condition precluding neoadjuvant treatment and surgical resection.
4. Previous chemotherapy ending < 3 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis).
5. Pregnancy.
6. WHO status 2-4.
7. New York Heart Association Classification Grade III or IV.
8. Uncontrolled Angina/ischaemic heart disease
9. Patients with known malabsorption.

The trial will be conducted in accordance with the information provided in the Summary of product characteristics of the trial Investigational Medicinal Products regarding contraindications and contraception (for both male and female participants).

5.1 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any
adverse event resolve or the subject’s condition becomes stable. Patients will be followed up 3-monthly from randomisation for one year as part of the trial, then followed up as part of standard care until death.

5.1.1 Patient Transfers

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 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.

5.1.2 Ending Trial Intervention Early

Patients may stop taking neoadjuvant treatment early for any of the following reasons:

a. Patient/legal representative withdraws consent.
b. Unacceptable toxicity.
c. Intercurrent illness preventing further treatment.
d. Any change in the patient’s condition that justifies the discontinuation of treatment in the clinician’s opinion.

If a patient wishes to discontinue neoadjuvant treatment, 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. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up.

If the patient commences trial treatment but it is stopped early due to a reaction or intolerance and they go on to have routine surgery, the surgery CRF should be completed. We will continue to follow the patient up as per the schedule unless they withdraw consent.

If the patient cannot commence trial treatment or have immediate surgery (ARM A), we follow the patient up as per schedule unless they withdraw consent. If at some point a patient in this category goes on to have routine surgery (i.e. if they have had a positive response to off-study treatment) we will not ask for the surgery CRF to be completed.

Patients who discontinued treatment early or patients who were re-scanned and found to be no longer borderline resectable should continue onto follow up however some trial interventions may not be applicable i.e CT scans.

5.1.3 Withdrawal from Trial Completely

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. Data up to this time can be included in the trial if anonymised. They may need to reaffirm that they consent to follow-up through usual NHS mechanisms. If the patient explicitly states their wish not to contribute further data to the study, a withdrawal CRF should be completed.

Discharge from the oncology department should not be considered the same as withdrawal from the trial. Patients should still be considered to be trial participants even if they are transferred to another department, such as to palliative care or to their family doctor.
6 ENROLMENT AND RANDOMISATION

Before a patient begins screening assessments for the main study, all patients will undergo a ‘Central Review’ of their CT scan to confirm that the patient meets the criteria for borderline resectable.

Multidetector CT images will be transferred from the participating centre to the Radiology department at the Royal Liverpool and Broadgreen University Hospital Trust and will be identifiable by unique screening number only. The participating centre should fax the following to the LCTU:

- ESPAC-5F Informed Consent Form (Central Review)
- ESPAC-5F CT Scan Review Baseline CRF
- Copy of the CT scan report

Confirmation of borderline resectability will be made by the next available working day following receipt of CT scans, CRFs and the participating centre informed.

Potential participants failing to meet the criteria for borderline resectability at central review will not subsequently be eligible to participate in the trial.

6.1 Screening

Screening will be performed upon a patient’s possible eligibility for the study and must be documented on the LCTU web portal “Screening and Enrolment log”. Screening details should be entered into the portal and this will automatically generate the screening number; a confirmation email with these details will be sent to site staff. The screening log can be printed off at any time from the LCTU Portal (www.LCTU.org.uk) to allow for storage in the Investigator Site File.

Step-by-step guides will be issued to research site staff and the process will also be demonstrated during site initiations.

Start of screening is defined as the patient being first discussed for eligibility at the local MDT meeting; this should be followed by the signing of the Informed Consent Form and, if eligible for the trial, randomisation. Patient hospitals notes should be screened by the research team prior to the patient being approached to ensure there are no obvious exclusion criteria and that the inclusion criteria can be met.

Laparoscopy may be carried out as part of screening according to standard local practice.

Chest X-rays may be carried out as per standard local practice.

6.2 Enrolment/ Baseline

Trial specific screening activities will be performed after patients have consented to trial participation and signed the informed consent form. Some investigations are performed routinely for the purposes of diagnosis and staging (before the trial is even considered) and these may also be used as screening assessments provided they are performed within the appropriate time frame (see section 8.1).

The following screening assessments should be performed:

- Written Informed Consent
- Confirmation of diagnosis (Histology/cytology)
- Complete Demography and medical history
- Concomitant medication
• Concurrent Medical Conditions
• Physical examination and Medical Review
• WHO performance status
• CT scan of chest, abdomen and pelvis
• Central confirmation of borderline resectable criteria
• Haematological / clinical chemistry
• Vital signs
• Translational Blood Samples
• CA19-9
• Pregnancy test (women of child-bearing potential only)

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 randomisation documents by the investigators:

• Completed Randomisation and Baseline Forms signed by an Investigator
• A copy of the Signed Consent Forms
• Anonymised copy of the pathology report
• Anonymised copy of screening haematology/serum chemistry
• A copy of the concomitant medication form and concurrent medical conditions form (if applicable)
• Completed Eligibility Checklist CRF signed by an Investigator

The randomisation documents should be faxed to the LCTU on Monday - Friday from 09:00 to 17:00 UK time, fax number: +44 (0) 151 794 8030. Prior to faxing documents, site staff should telephone +44 (0) 151 794 8935 / 795 5294 to inform the LCTU staff of the incoming randomisation fax.

<< Randomisation tel. +44 (0) 151 794 8834 / fax number +44 (0) 151 794 8930 >>
(Note that the LCTU is open from 09:00 – 17:00 UK time, Monday – Friday, excluding public holidays)
7 TRIAL TREATMENTS

7.1 Introduction

Patients will be randomised to either:

**ARM A** (immediate surgery)

Or

**ARM B** (Gemcitabine, 1000mg/m² iv infusion over 30 minutes, on days 1, 8 and 15 of a 28 day cycle plus Capecitabine 830mg/m² BD PO for 21 out of 28 days (one cycle), for 2 cycles (total of 8 weeks))

Or

**ARM C** (Oxaliplatin 85mg/m², Irinotecan 180mg/m², Folinic acid given as per local practice for both the drug and dose, 5-FU 400mg/m² bolus injection followed by 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles for a total of 8 weeks)

Or

**ARM D** (CRT delivering a total dose of 50.4Gy in 28 daily fractions over 5½ weeks (1.8Gy/# Mon – Fri) with Capecitabine 830mg/m² BD PO (Mon – Fri) throughout Radiotherapy).

For the purposes of this study, all the drugs listed above are considered IMPs.

7.2 Arm A: Immediate Surgery

Eligible patients will undergo surgical exploration for resection. Minimum standards will apply – agreed by the surgical working party and incorporated into the ESPAC-5F Surgical Handbook (**SSES5F_D031**). All investigators will attend workshops run from the co-ordinating centre (Liverpool) which will incorporate live operating sessions, videos and question and answer sessions.

Patients will undergo a pylorus preserving or classical Kausch Whipple resection with standard lymphadenectomy [33,34,43]. Total pancreatectomy will be accepted if clinically indicated. Venous resection and or reconstruction will be performed when clinically indicated at the discretion of the PI [44]. Arterial resection/reconstruction will not be allowed in the protocol.

Photographs will be taken of the operative field following resection and a surgical proforma will be completed. If the tumour is not resectable, the reasons why will be documented on the surgical proforma and photographs of the operative field will be taken. Gastric bypass with or without biliary bypass will be performed [45] as clinically indicated.

Peri-operative complications, post-operative complications [36-38] and 30 day mortality will be recorded. Each surgeon at the centre will attend the surgical workshop and be given a surgical handbook detailing minimum acceptable standards for the surgical procedures.
7.3 Arm B: GemCap

7.3.1 Formulation, Packaging, Labelling, Storage and Stability

Gemcitabine

Gemcitabine is a nucleoside analogue interfering with DNA replication.

Manufacturer: 
Generic gemcitabine can be sourced by pharmacies following their usual local practice, including premade supplies. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites. 

Formulation: 
Lyophilised power for solution for intravenous infusion or as a concentrate for solution for 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 powder 
Gemcitabine / 38mg/ml and 100mg/ml concentrate

Please refer to current Gemcitabine SmPCs supplied by the appropriate manufacturer, which may be found below:

www.medicines.org.uk/emc/search/?q=Gemcitabine&dt=1

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 can be sourced by pharmacies following their usual local practice. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites. 

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, which may be found below:

www.medicines.org.uk/emc/search/?q=Capecitabine&dt=1
7.3.2 Preparation, Dosage and Administration of Study Treatments

Gemcitabine

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), or local practice:

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

- (Re-)Calculate the exact (not rounded) target dose of gemcitabine, based on the BSA at the start of each cycle
- Bloods for toxicity assessment may be taken up to two days prior to the start of each week of treatment and the dose should take into account any toxicity found (see section 7.3.3).
- Use Table 2 below to find the rounded dose category and the dose to be administered:

Table 2

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

- Where the above dose banding or BSA calculation cannot be followed exactly at a Research Site, local practice can be followed including all volumes, fluids and administration times. This must be clearly documented in the Research Site Pharmacy File and a copy of the procedures sent to the co-ordinating centre (LCTU). ALL doses must be within 7% of dose listed in Table 2.

- Doses calculated and dispensed not according to the ESPAC-5F 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.
Capecitabine

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

www.medicines.org.uk/emc/search/?q=Capecitabine&dt=1

and according to local policies.

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):

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

- (Re-)Calculate the dose based on the BSA at the start of each cycle and use Table 3 below to find the rounded dose category and the number of tablets per dose:

<table>
<thead>
<tr>
<th>Body surface area (m²)</th>
<th>Total daily dose (mg)</th>
<th>Number of tablets administered in the morning</th>
<th>Number of tablets administered in the evening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150mg</td>
<td>500mg</td>
<td>150mg</td>
</tr>
<tr>
<td>&lt; 1.60</td>
<td>2500</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1.60 – 1.80</td>
<td>2800</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 1.80</td>
<td>3300</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**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 practice can be followed including all volumes, fluids and administration times. This must be clearly documented in the Research Site Pharmacy File and a copy of the procedures sent to the co-ordinating centre (LCTU). **ALL** doses must be within 7% of dose listed in Table 3.

- Doses calculated and dispensed not according to the ESPAC-5F 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.
7.3.3 Dose Modifications

7.3.3.1 Gemcitabine

1000mg/m² gemcitabine must be given as an intravenous infusion, the lyophilized powder being diluted in normal saline (gemcitabine may be bought as a pre-prepared vial/bag) over 30 minutes unless haematological toxicity occurs requiring dose adjustment as described below. Administer on days 1, 8 and 15 (one cycle) for two cycles i.e. 8 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.

On the day of gemcitabine administration, the following dose should be given according to the absolute neutrophil and platelet counts on that day (or having been measured within 48 hours previously):

Table 4: Neutrophil Toxicity – Dose Adjustment

<table>
<thead>
<tr>
<th>Absolute neutrophil count (x10⁹/l)</th>
<th>Gemcitabine dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.0</td>
<td>100% of full dose</td>
</tr>
<tr>
<td>0.5 – 0.99</td>
<td>75% of full dose</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Omit for one week</td>
</tr>
</tbody>
</table>

Table 5: Platelet Toxicity – Dose Adjustment

<table>
<thead>
<tr>
<th>Platelet count (x10⁹/l)</th>
<th>Gemcitabine dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100</td>
<td>100% of full dose</td>
</tr>
<tr>
<td>50 – 100</td>
<td>75% of full dose</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Omit for one week</td>
</tr>
</tbody>
</table>

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 6 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.

Table 6: Haematological dose modification

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

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).
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 (prophylactically, if it is local practice) neutropenic sepsis and/or as secondary prophylaxis with subsequent cycles, according to usual local practice. 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.

**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.
7.3.3.2 Capecitabine

- 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 approximately 1660mg/m² (depending, of course, on the dose banding) must be administered unless toxicity occurs requiring dose adjustment as described below.

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.

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 instigated as necessary; loperamide, pyridoxine and emollients, sulcrulfate etc.

The following dose modification of capecitabine refers to non-haematological toxicities: Haematological toxicity due to capecitabine is rare. Where haematological toxicity is encountered, the guidance in Table 7 should be followed.

**Table 7: Dose Modification for Capecitabine**

<table>
<thead>
<tr>
<th>Grading according to NCI-CTCAE v4</th>
<th>Occurrence</th>
<th>Action</th>
<th>Dose adjustment for next cycle (% of starting dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Supportive measures</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>First appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Second appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Third appearance</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Grade 3</td>
<td>First appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Second appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Third appearance</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Grade 4</td>
<td>First appearance</td>
<td>Discontinue permanently</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>
Renal Impairment

During the study, creatinine clearance should be calculated. For patients with mild renal impairment (creatinine clearance 51-80 ml/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 chemotherapy and considered for surgery.

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 ≤ 3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN.

Haematological toxicity due to capecitabine is rare. Where haematological toxicity is encountered, the guidance in Table 7 (above) should be followed.

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

Table 8: For patients with a body surface area < 1.60m².

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Total daily dose (mg)</th>
<th>Number of tablets administered in the morning</th>
<th>Number of tablets administered in the evening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>150mg</td>
<td>500mg</td>
</tr>
<tr>
<td>100%</td>
<td>2500</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>75%</td>
<td>1800</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50%</td>
<td>1300</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 9: For patients with a body surface area between 1.60m² and 1.80m².

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Total daily dose (mg)</th>
<th>Number of tablets administered in the morning</th>
<th>Number of tablets administered in the evening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>150mg</td>
<td>500mg</td>
</tr>
<tr>
<td>100%</td>
<td>2800</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>75%</td>
<td>2150</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>50%</td>
<td>1450</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 10: For patients with a body surface area > 1.80m².

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Total daily dose (mg)</th>
<th>Number of tablets administered in the morning</th>
<th>Number of tablets administered in the evening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>150mg</td>
<td>500mg</td>
</tr>
<tr>
<td>100%</td>
<td>3300</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>75%</td>
<td>2500</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>50%</td>
<td>1650</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
- 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 (whether previously known to have controlled angina or not) whilst receiving capecitabine, then treatment should be suspended immediately pending further clinical assessment. If the chest pain is deemed to be capecitabine related, then the patient should not recommence treatment with capecitabine.

**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 Arms B and D due to the 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.

**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.
7.4 Arm C: FOLFIRINOX

7.4.1 Formulation, Packaging, Labelling, Storage and Stability

Medications in the FOLFIRINOX regimen may be dose banded if it is local policy. This must be clearly documented in the Research Site Pharmacy File and a copy of the procedures sent to the co-ordinating centre (LCTU).

5-Fluorouracil

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

**Manufacturer:** Generic 5-Fluorouracil can be sourced by pharmacies following their usual local practice, including premade supplies. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites. [http://emc.medicines.org.uk](http://emc.medicines.org.uk), [www.mhra.gov.uk](http://www.mhra.gov.uk), [www.ema.europa.eu](http://www.ema.europa.eu)

**Formulation:** Solution for injection

**Packaging, Storage and Stability:** Please refer to the specific SmPC for individual product

**Supplier’s Name:** The local hospital pharmacy

**Active Ingredient Name /Dose:** 500 mg fluorouracil in 10 ml solution

Please refer to current Fluorouracil SmPCs supplied by the appropriate manufacturer: [www.medicines.org.uk/emc/search/?q=Fluorouracil&dt=1](http://www.medicines.org.uk/emc/search/?q=Fluorouracil&dt=1)

(Re-)Calculate the dose based on the BSA measured at the start of each cycle.

Folinic Acid

Folinic acid is a 5-formyl derivative of tetrahydrofolic acid. Folinic acid is used in combination with the chemotherapy agent 5-fluorouracil. It enhances the effect of 5-fluorouracil by inhibiting thymidylate synthase.

**Manufacturer:** Generic Folinic Acid can be sourced by pharmacies following their usual local practice, including premade supplies. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites. [http://emc.medicines.org.uk](http://emc.medicines.org.uk), [www.mhra.gov.uk](http://www.mhra.gov.uk), [www.ema.europa.eu](http://www.ema.europa.eu)

**Formulation:** Solution for injection

**Packaging, Storage and Stability:** Please refer to the specific SmPC for individual product

**Supplier’s Name:** The local hospital pharmacy

**Active Ingredient Name /Dose:** Sodiumfolin 50 mg/ml, solution for injection or infusion

Calcium Folinate 10 mg/mL Injection

Please refer to current Folinic Acid guidelines.

Folinic acid SmPCs supplied by the appropriate manufacturer: [www.medicines.org.uk/emc/search/?q=Folinic%20Acid&dt=1](http://www.medicines.org.uk/emc/search/?q=Folinic%20Acid&dt=1)

(Re-)Calculate the dose based on the BSA measured at the start of each cycle.
Irinotecan
Irinotecan is a topoisomerase I inhibitor.

**Manufacturer:**
Generic Irinotecan can be sourced by pharmacies following their usual local practice, including premade supplies. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites:


**Formulation:**
Concentrate For Solution For 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:**
Each ml contains 20 mg irinotecan hydrochloride trihydrate, equivalent to 17.33 mg irinotecan.

Please refer to current Irinotecan SmPCs supplied by the appropriate manufacturer:
www.medicines.org.uk/emc/search/?q=Irinotecan&dt=1

(Re-)Calculate the dose based on the BSA measured at the start of each cycle.

Oxaliplatin
Oxaliplatin is an antineoplastic active substance belonging to a class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group. It interacts with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

**Manufacturer:**
Generic Oxaliplatin can be sourced by pharmacies following their usual local practice, including premade supplies. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites:


**Formulation:**
Solution for injection

**Packaging, Storage and Stability:**
Please refer to the specific SmPC for individual product

**Supplier’s Name:**
The local hospital pharmacy

**Active Ingredient Name / Dose:**
One ml of reconstituted solution contains oxaliplatin 5 mg.

Please refer to current Oxaliplatin SmPCs supplied by the appropriate manufacturer:
www.medicines.org.uk/emc/search/?q=Oxaliplatin&dt=1

(Re-)Calculate the dose based on the BSA measured at the start of each cycle.
7.4.2 Preparation, Dosage and Administration of Study Treatments

Oxaliplatin

Oxaliplatin must be handled and stored according to the instructions in SmPC supplied by the appropriate manufacturer.

www.medicines.org.uk/emc/search/?q=Oxaliplatin&dt=1

- 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) or local practice:

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

Oxaliplatin at a dose of 85 mg/m\(^2\) given as a 2 hour intravenous infusion

- Bloods for toxicity assessment may be taken up to two days prior to the start of each week of treatment and the dose should take into account any toxicity found (see section 7.4.3).

Oxaliplatin should always be administered before fluoropyrimidines - i.e. 5 fluorouracil (5 FU).

Oxaliplatin powder for solution for infusion is administered as a 2 hour intravenous infusion in 250 to 500 ml of glucose 5% solution (50 mg/ml) to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m\(^2\).

Folinic acid

Folinic acid must be handled and stored according to the instructions in SmPC supplied by the appropriate manufacturer.

www.medicines.org.uk/emc/search/?q=Folinic%20Acid&dt=1

- 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) or local practice:

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

Folinic acid at a dose determined by local practice, given as a 2-hour intravenous infusion. Folinic acid should be prepared and administered as per local practice. Preparation of solution for infusion must take place in aseptic conditions.

Solution for injection or infusion as a 2 hour intravenous infusion concurrently with oxaliplatin (or as per local policy).

Folinic acid 50 mg/ml is compatible with fluorouracil.
**Irinotecan**

Irinotecan must be handled and stored according to the instructions in SmPC supplied by the appropriate manufacturer.

[www.medicines.org.uk/emc/search/?q=Irinotecan&dt=1](http://www.medicines.org.uk/emc/search/?q=Irinotecan&dt=1)

- 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):

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

Irinotecan at a dose of 180 mg/m\(^2\), given as a 90-minute intravenous infusion.

Irinotecan concentrate for solution for infusion is intended for intravenous infusion only after diluting prior to administration in the recommended diluent: 0.9 % Sodium chloride solution for infusion. Aseptically withdraw the required amount of Irinotecan concentrate for solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle.

Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

**5-Fluorouracil**

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

[www.medicines.org.uk/emc/search/?q=Fluorouracil&dt=1](http://www.medicines.org.uk/emc/search/?q=Fluorouracil&dt=1)

and according to local policies.

- 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) or local practice:

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

5-FU 400mg/m\(^2\) bolus injection followed by 2400mg/m\(^2\) 46 hour infusion.

Selection of an appropriate dose and treatment regime depend upon the condition of the patient, the type of carcinoma being treated and whether Fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with patient’s actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight is used as the basis for calculation. Reduction of the dose is advisable in patients with any of the following:

1. Cachexia.
2. Major surgery within preceding 30 days.
3. Reduced bone marrow function.
4. Impaired hepatic or renal function.

Fluorouracil Injection can be given by intravenous injection or, intravenous or intra-arterial infusion.
7.4.3 Dose Modifications

FOLFIRINOX: dose modifications for toxicity (modified from Conroy et al)

All dose adjustments to be made based on worst preceding toxicity.

Dose of folinic acid is not modified for toxicity, but should be omitted if is 5-FU omitted.

Following a dose reduction, no re-escalation is permitted.

If the same grade 4 toxicity occurs despite appropriate dose reductions, discontinue FOLFIRINOX.

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 withdraws from treatment should remain on follow-up within the trial.7

7.4.3.1 Haematological Toxicity

Doses based on full blood count on day 1 of each cycle.

Do not re-treat until neutrophils ≥ 1.0x10⁹/L and platelets ≥ 75x10⁹/L

Table 11

<table>
<thead>
<tr>
<th>Blood count on day 1</th>
<th>Delay of cycle</th>
<th>Dose reduction</th>
<th>irinotecan</th>
<th>oxaliplatin</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils &lt;1.0x10⁹/L</td>
<td>Hold all chemo until neutrophils ≥ 1.0x10⁹/L</td>
<td>1st occurrence</td>
<td>Reduce to 150mg/m²</td>
<td>No reduction</td>
<td>No reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd occurrence</td>
<td>Continue at 150mg/m²</td>
<td>Reduce to 60mg/m²</td>
<td>No reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd occurrence</td>
<td>Discontinue FOLFIRINOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If not recovered ≥ 1.0x10⁹/L after 2 weeks delay</td>
<td>Discontinue FOLFIRINOX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;75x10⁹/L</td>
<td>Hold all chemotherapy until platelets ≥ 75x10⁹/L</td>
<td>1st occurrence</td>
<td>No reduction</td>
<td>Reduce to 60mg/m²</td>
<td>Reduce to 75% original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd occurrence</td>
<td>Reduce to 150mg/m²</td>
<td>Continue at 60mg/m²</td>
<td>Continue at 75% dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd occurrence</td>
<td>Discontinue FOLFIRINOX</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If not recovered ≥ 75x10⁹/L after 2 weeks delay</td>
<td>Discontinue FOLFIRINOX</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 12

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Dose reduction for subsequent cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>b) Grade 4 neutropenia lasting &gt; 7 days</td>
<td></td>
</tr>
<tr>
<td>c) Infection with grade 3/4 neutropenia</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence</td>
<td>Reduce irinotecan to 150mg/m²</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; occurrence</td>
<td>Continue irinotecan at 150mg/m², and Reduce oxaliplatin to 60mg/m²</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>Discontinue FOLFIRINOX</td>
</tr>
<tr>
<td>Grade 3/4 thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence</td>
<td>Reduce oxaliplatin to 60mg/m², And Reduce 5-FU to 75% original dose</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; occurrence</td>
<td>Continue oxaliplatin at 60mg/m², And Reduce irinotecan to 150mg/m² And Reduce 5-FU by a further 25%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>Discontinue FOLFIRINOX</td>
</tr>
</tbody>
</table>

If not already used, consider G-CSF for recurrent grade 3/4 neutropenia despite first dose reduction or after any febrile neutropenia

#### 7.4.3.2 Gastrointestinal Toxicity

Patients must be instructed on the use of loperamide for diarrhoea and must be prescribed a supply loperamide upon commencing FOLFIRINOX. As per section 7.9, local practice should be followed for supportive medication.

Re-treatment with irinotecan should not occur until resolution of diarrhoea for >24 hours

### Table 13

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Dose reduction for subsequent cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea grade ≤³</td>
<td></td>
</tr>
<tr>
<td>Or Diarrhoea + fever +/- grade 3/4 neutropenia</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; occurrence</td>
<td>Reduce irinotecan to 150mg/m²</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; occurrence</td>
<td>Continue irinotecan at 150mg/m², and Reduce oxaliplatin to 60mg/m² And Reduce 5-FU to 75% original dose</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>Discontinue FOLFIRINOX</td>
</tr>
</tbody>
</table>

#### 7.4.3.3 Mucositis

Grade 3/4 mucositis: reduce 5-FU to 75% original dose.
7.4.3.4 Hand-Foot Skin Reactions

Grade 3/4 HFS: reduce 5-FU to 75% original dose.

7.4.3.5 Cardiac

If patients develop angina-like pain whilst receiving 5-FU, then treatment should be suspended immediately pending further clinical assessment. If angina is confirmed then the 5-FU should be discontinued. Also in event of myocardial infarction, discontinue 5-FU.

7.4.3.6 Hyperbilirubinaemia

Exclude biliary obstruction or progressive disease. If bilirubin > 1.5 x ULN, irinotecan is not recommended.

7.4.3.7 Other Toxicities

For any other toxicity ≥ grade 2 (except anaemia, alopecia), adjust doses if medically indicated. For example, depending on type of adverse event:

Reduce irinotecan to 150mg/m²
And/or
Reduce oxaliplatin to 60mg/m²
And/or
Reduce 5-FU to 75% original dose.

7.4.3.8 Other Oxaliplatin-Related Toxicities

Renal impairment

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity.

Hypersensitivity reactions

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

In case of oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.

Neurological symptoms

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.
Peripheral neuropathy

If neurological symptoms (paraesthesia, dysesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 60 mg/m².
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 60 mg/m².
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibilities of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate parasthesias or paraesthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8 of the SmPC). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration and haematological changes

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8 of the SmPC).

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emas infusion particularly when combining oxaliplatin with 5-fluorouracil.

Pulmonary

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8 of the SmPC).

Hepatic

In cases of abnormal test results of liver function or portal hypertension, which does not obviously depend on liver metastases, very rare cases of drug induced hepatic vascular disorder should be considered.
7.5  **Arm D: Chemoradiotherapy**

7.5.1  **Introduction**

This radiotherapy protocol has been developed by radiation oncologists, research radiographers and physicists who are members of the ESPAC5 RT working party and has been peer reviewed by independent pancreatic radiation oncologists.

The key references for this work are the existing SCALOP RT protocol (Mukherjee et al, Lancet Oncol, March 2013) and the pancreatic RT consensus document (Abrams et al, IJROBP, 2012). This document outlines the key principles – investigators should refer to the detailed ESPAC5 radiotherapy planning and delivery guideline document which has also been developed and will be made available on the NCRI RTTQA website (www.rttrialsqa.org.uk/).

7.5.2  **Optional Pre-Radiotherapy Investigations**

If considered local standard of care additional diagnostic assessments, as per institutional practice, may be of assistance in identifying disease not visible on CT and distinguishing pancreatic tumour from duodenum, but GTV defined by diagnostic CT scan must not be reduced based on these optional investigations alone.

7.5.3  **MAG3 Renogram and EDTA Clearance**

MAG3 renogram and EDTA clearance to assess renal function recommended (but not mandated).

7.5.4  **Radiotherapy Dose prescription**

Bloods for toxicity assessment may be taken up to two days prior to the start of each week of treatment and the dose should take into account any toxicity found (see section 7.5.9).

The dose to the PTV will be 50.4Gy in 28 fractions (1.8Gy per fraction) treating once daily, 5 days per week, using photon beams of 6MV or higher. Ninety-five percent of the PTV must receive at least 93% of the dose. The maximum dose allowed within the PTV to a point that is 0.01 cc is 107% of the prescribed dose.

7.5.5  **Radiotherapy Technique**

Intensity Modulated RT (IMRT) is preferred over 3D conformal RT but prior IMRT accreditation is necessary through the NCRI RTTQA group or European equivalent.

7.5.6  **Radiotherapy Treatment Planning and Delivery**

Refer to the Radiotherapy Treatment Planning and Delivery document (available on the RTTQA website) for details regarding:

- Radiotherapy localisation, simulation and immobilisation
- Target volume delineation including organs at risk (OARs)
- Dose constraints to planning target volume and OARs
- Treatment verification
- Radiotherapy quality assurance
7.5.7 Concurrent Chemotherapy

- 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):

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

Capecitabine 830mg/m\(^2\) twice daily to be taken orally on days of RT only (Monday to Friday).

**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 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.

7.5.8 Management of Unscheduled Gaps in Radiotherapy Treatment

This will be managed in line with the latest RCR guidance, which may be found at the link below.

[www.rcr.ac.uk/docs/oncology/pdf/BFCO(08)6_Interruptions.pdf](http://www.rcr.ac.uk/docs/oncology/pdf/BFCO(08)6_Interruptions.pdf)

Acceptable interruptions:

Per protocol: 0-7 days
Variation acceptable: 8-14 days.
Deviation unacceptable: >14 days

7.5.9 Adverse Effects of Radiotherapy

- Nausea
- Vomiting
- Diarrhoea
- Fatigue
- Weight loss
- Oesophagitis
- Gastritis
- Gastro-intestinal ulceration
- Gastro-intestinal haemorrhage
- Gastro-intestinal perforation
- Gastro-intestinal fistula
- Intestinal obstruction
- Radiation dermatitis
- Second malignancy (rare)
7.5.9.1 Management of Haematological Toxicity During Chemoradiation

Table 14

<table>
<thead>
<tr>
<th>Neutrophil * (x 10^9/l)</th>
<th>Platelet * (x 10^9/l)</th>
<th>Capecitabine arm</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0</td>
<td>&gt;75</td>
<td>100% dose</td>
<td>Continue</td>
</tr>
<tr>
<td>0.5 - &lt;1.0</td>
<td>50 -75</td>
<td>Withhold until neutrophils ≥1.0 AND platelets &gt;75, then re-commence at 75% dose</td>
<td>Continue</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>&lt;50</td>
<td>1st episode: Omit dose for the week. Subsequent dose at 75% 2nd episode: Omit dose for a week. Subsequent dose at 50%. 3rd episode: Omit capecitabine</td>
<td>Withhold RT. Repeat FBC in 3 days. Restart RT alone when neutrophils ≥0.5 AND platelets ≥50</td>
</tr>
</tbody>
</table>

* Dose reduction to be made based on the worse of the two blood parameters

7.5.9.2 Management of Gastro-intestinal Toxicity During Chemoradiation

Table 15

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Capecitabine</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea / vomiting</td>
<td>Grade 1 and Grade 2</td>
<td>Full dose. Maximise anti-emetic support</td>
<td>Continue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 despite maximum anti-emetic support for 24 hours and Grade 3</td>
<td>Withhold until G1. 1st episode: Restart at 625mg/m² BD 2nd episode: Restart at 415 mg/m² (50%) BD 3rd episode: Discontinue</td>
<td>Continue for 1st episode. For subsequent episodes, withhold until G1</td>
</tr>
<tr>
<td>Diarrhoea (non-pancreatic)</td>
<td>Grade 1 and Grade 2</td>
<td>Full dose. Optimize anti-diarrhoeal support.</td>
<td>Discontinue</td>
</tr>
<tr>
<td></td>
<td>Grade 2 despite anti-diarrhoeal support for 24 hours and Grade 3</td>
<td>Withhold until G1. 1st episode: Restart at 625mg/m² BD 2nd episode: Restart at 415 mg/m² (50%) BD 3rd episode: Discontinue</td>
<td>Continue for 1st episode. For subsequent episodes, withhold until G1</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

7.5.9.3 Management of Other Non-haematological Toxicity During Capecitabine Therapy

For any other information regarding capecitabine, including dose banding, drug interactions, dose adjustment for hepatic and renal compromise, please refer to the relevant parts of section 7.3, Arm B: GemCap.
7.6 Unblinding
Not applicable.

7.7 Accountability Procedures for Study Treatments
The PI is fully responsible for the Investigational Medicinal Products (IMPs) at the site. Dispensing of medication may be delegated to a hospital pharmacy as locally applicable. The person responsible for dispensing the medication will be responsible for maintaining adequate control of the IMPs and for documenting all transactions relating to them (as a minimum batch number, expiry date and dispense date must be documented on the LCTU Drug Accountability Logs). IMPs must be stored in a safe and secure place (only accessible to authorized personnel), and proper dispensing arrangements must be made.

7.8 Assessment of Compliance with Study Treatments
The majority of trial treatment will be administered during hospital outpatient visits, ensuring accurate monitoring of gemcitabine, folfirinox and radiotherapy 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. Patients will be issued with treatment diaries to record compliance with home treatment regimens and asked if they had any difficulties with the previous cycle of treatment. Nursing staff will collect the used and unused sheets, which will be returned to pharmacy, where the number of returned tablets should be documented on the patient accountability log.

7.9 Concomitant Medications / Treatments
Concomitant treatment for conditions other than pancreatic ductal adenocarcinoma 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. Supportive medications should be administered as per local practice.

7.9.1 Medications Permitted
All medication necessary for the wellbeing 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.

7.9.2 Medications Not Permitted / Precautions Required
Gemcitabine
For medications not permitted / precautions required for gemcitabine, the most current SmPC should be referred to.

Radiotherapy
Concurrent (given together or ≤7 days apart) - Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of gemcitabine, frequency of gemcitabine administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume. Pre-clinical and clinical studies have shown that gemcitabine has radiosensitising activity which can result in significant and potentially life
threatening toxicity. The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined in all tumour types.

Non-concurrent (given >7 days apart) - Analysis of the data does not indicate any enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation, other than radiation recall. Data suggest that gemcitabine can be started after the acute effects of radiation have resolved or at least one week after radiation.

Radiation injury has been reported on targeted tissues (e.g., oesophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine.

Yellow fever and other live attenuated vaccines are not recommended due to the risk of systemic, possibly fatal, disease, particularly in immunosuppressed patients.

**Capecitabine**

For medications not permitted/precautions required for capecitabine, the most current SmPC should be referred to.

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 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.

Since current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. Administration with food decreases the rate of capecitabine absorption

**Oxaliplatin**

For medications not permitted/precautions required for Oxaliplatin, the most current SmPC should be referred to.

**Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.**

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed. *In vitro*, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.
**Irinotecan**

For medications not permitted/precautions required for Irinotecan, the most current SmPC should be referred to.

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

Co-administration of atazanavir sulphate, has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided.

St. John’s Wort should not be administered with irinotecan.

Concomitant use contraindicated:

Yellow fever vaccine: risk of fatal generalised reaction to vaccines

Concomitant use not recommended:

Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease (e.g. infections). This risk is increased in subjects who are already immunosuppressed by their underlying disease

Use an inactivated vaccine where this exists (poliomyelitis)

Phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement due to increased hepatic metabolism by phenytoin

Concomitant use to take into consideration:

Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation

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**5-Fluorouracil**

For medications not permitted/precautions required for 5-Fluorouracil, the most current SmPC should be referred to.

5-Fluorouracil (5-FU) must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin and analogues are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD)
Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin.

Various agents have been reported to biochemically modulate the anti-tumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, Folinic acid interferon alfa and allopurinol.

Fluorouracil should be avoided in combination with clozapine due to increased risk of agranulocytosis.

Marked elevations of prothrombin time and INR have been reported in patients stabilised on warfarin therapy following initiation of Fluorouracil regimes.

Cimetidine has been reported to increase plasma concentrations of Fluorouracil, possibly by reduced hepatic metabolism.

Vaccination with live vaccines should be avoided in immune compromised patients.

**Folinic acid**

For medications not permitted/precautions required for folinic acid, the most current SmPC should be referred to.

Concomitant use of disodium folinate counteracts the antineoplastic activity of methotrexate and increases the cytotoxic effects of fluorouracil.

Concomitant use requiring precautions for use: Phenobarbital, primidone, phenytoine: decreased plasma levels of enzymatic inductor anti-convulsant drugs by increasing the hepatic metabolism for which folates are one of the cofactors

When calcium folinate is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Calcium folinate may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also sections 4.4 and 4.8).

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil.

### 7.9.3 Data on Concomitant Medication

Dose and names of all concomitant medication should be documented on the CRF at screening. This will be reassessed by the PI throughout trial participation during clinical review. Any new medications introduced or changes to medications during the trial period should be documented on the CRF.
7.10 Overdoses

Gemcitabine

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.

Capecitabine

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.

5-Fluorouracil

Manifestations of overdosage of fluorouracil can be nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilised.

Folinic acid

Should overdosage of the combination of fluorouracil and folinic acid occur, overdosage instructions for fluorouracil should be followed.

Irinotecan

There have been reports of overdosage, at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no known antidote for irinotecan. Maximum supportive treatment should be initiated to prevent dehydration due to diarrhoea and to treat any infectious complications.

Oxaliplatin

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

7.11 Co-enrolment Guidelines

Not applicable
8 ASSESSMENTS AND PROCEDURES

8.1 Schedules of Trial Procedures
### Table 16: Arm A: Immediate Surgery

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<th>Screening and baseline</th>
<th>Rand</th>
<th>Surgery</th>
<th>Post-surgery</th>
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* +/– 2 weeks; # +/- 1 week; $ if it is local practice.

### Table 17: Arm B: Gemcitabine plus Capecitabine

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A confidential CR-UK Liverpool Cancer Trials Unit document

ESPAC-5F Protocol, Version 6.0, 27/01/2017
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* +/- 2 weeks; # +/- 1 week; Gemcitabine: 1000mg/m² iv infusion over 30 minutes, day 1, 8 and 15 of a 28 day cycle for 2 cycles, Capecitabine: 830mg/m² BD PO for 21 out of a 28 day cycle for 2 cycles; £ Bloods measuring toxicity should be taken on the day or within 48 hours prior the start of each week of treatment. ** Bloods for translational study required Day 8 (Cycle 1 only); @ In addition to bloods for translational study patients in Arm B Immune response sub group (Liverpool only) will provide sodium heparin bloods samples at the time points specified; ^ Only applicable to Royal Liverpool University Hospital patients; $ If it is local practice; † if clinically indicated, as per local standard practice.
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*$4$ weeks = 28 days, $1$ week = 7 days, $2$ day = 2 days
## Procedures

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* +/- 2 weeks; # +/- 1 week; + Oxaliplatin 85mg/m², Irinotecan 180mg/m², Folinic acid per local practice, 5-FU 400mg/m² bolus injection followed by 2400mg/m² 46 hour infusion, repeated every 2 weeks for 4 cycles; # +/- 1 week; £ Bloods measuring toxicity should be taken on the day or within 48 hours prior the start of each week of treatment; ** Bloods for translational study required Day 1 (Cycle 2, Cycle 3 and Cycle 4 only); ^ Cycles 1 and 3 only; $ If it is local practice.
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<td>EUS FNA for translational study</td>
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<tr>
<td>Procedures</td>
<td>Baseline and screening</td>
<td>Rand</td>
<td>RT planning</td>
<td>Radiotherapy cycle = 7 days (5 treatment 2 rest) – total 5 ½ cycles i.e. 38 days</td>
<td>Re-stage patient</td>
<td>Surgery</td>
<td>Post - surgery</td>
<td>Follow up 1</td>
<td>Follow up 2</td>
<td>Follow up 3</td>
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<td>Study withdrawal</td>
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<td>Blood for translational study</td>
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<td>RT Wk 1</td>
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<td>Randomise</td>
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<td>RT Wk 2</td>
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<td>Radiotherapy (IMRT/3D)</td>
<td>x</td>
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<td>RT Wk 3</td>
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<td>Resection – recover</td>
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<td>Pathology central core lab review</td>
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<td>Quality of life</td>
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<td>Complete End of Study CRF</td>
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</tbody>
</table>

* +/- 2 weeks; # +/- 1 week; + RT to commence on Monday to Friday for five days: total of 50.4Gy in 28 daily fractions over 28 days – equivalent of five weeks and three days; & Cycle 1 only; £ Bloods measuring toxicity should be taken on the day or within 48 hours prior the start of each week of treatment; ** Bloods for translational study required Day 1 (RT Week 2, RT Week 4 and RT Week 6 only); $ if it is local practice; ! if clinically indicated, as per local standard practice
8.2 Procedures for Assessing Efficacy

Resection rate (R1 + R0)
Resection rate will be measured using the total number of patients in the arm as baseline and, secondly, using the number of patients having explorative surgery. R1 and R0 resection margins will be included in the resection rate but not R2 resection.

R0 resection margin rate
R0 resection rate will be recorded according to the Royal College of Pathologists report on Standards and datasets for reporting cancers [47].

Post-operative complication rate
Post-operative morbidity will be recorded following surgery and classified according to existing guidelines [36-38].

Post-operative mortality rate
Post-operative mortality rate will be recorded as the 30 day mortality rate.

Response rate
Response will be assessed in accordance with RECIST 1.1 Guidelines [41], www.recist.com/files/Recist-1.1-Fanbook.pdf, and the proportions of patients achieving complete or partial responses and disease control will be compared across treatments using descriptive statistics (with 95% confidence intervals) and using Pearson’s chi-square test with continuity correction, Fishers Exact test or equivalent.

Disease free survival rate
DFS will be defined as number of days between date of surgery and disease recurrence (CT scan, +/- clinical assessment +/- CA19.9).

Local disease free survival rate
Local DFS will be defined as number of days between date of surgery and local disease recurrence (CT scan).

Overall survival
OS will be defined as the 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).

8.3 Procedures for Assessing Safety

Toxicity
Safety will be assessed through the reporting of adverse events as described in section 13. Formal toxicity assessments will be performed at each study visit as described in section 9. Adverse events will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4, which can be accessed at the following website:


8.4 Other Assessments

8.4.1 Quality of Life

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This is a generic cancer instrument composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social and cognitive function), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). All scales and single items meet the required standards for reliability and validity.
Patients are eligible for the QoL assessment in this study if they fulfil the eligibility criteria and complete the baseline QoL questionnaires before randomisation. Patients will be informed in the patient informed consent form that they will have their QoL assessment regularly while involved in this trial. Patients will be asked to complete QoL questionnaires according to the Table of Assessments in Section 8.

Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is approximately 10-15 minutes. The clinical forms will include a question whether the QoL forms have been filled in - and if not, the reason why. Follow up questionnaires will be completed on a monthly basis whilst on treatment.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

- a high score for a symptom scale or item represents a high level of symptoms or problems;
- a high score for a functional scale represents a high or healthy level of functioning and
- a high score for the global health status/QoL represents high QoL.

### 8.4.2 Special Assays or Procedures

Not applicable.

### 8.5 Translational Study

The neoadjuvant arms of ESPAC-5F provide an opportunity to evaluate theoretical or empirical markers of drug response or prognosis associated with GEMCAP, FOLFIRINOX and chemoradiotherapy. Some patients with borderline resectable pancreatic cancer will respond to neoadjuvant gemcitabine plus capecitabine or FOLFIRINOX or chemoradiation prior to undergoing surgical exploration. This may result in better resection rates and a survival benefit compared with patients who undergo immediate surgical exploration. The aim of the translational arm of this study is to facilitate the identification of markers in the primary tumour or blood which predict: (i) response/resistance (ii) the presence of micro-metastases and (iii) a survival benefit in patients recruited to the ESPAC-5F trial.

For the translational study, serum, plasma and cells will be collected from blood before, during and after neoadjuvant therapy, post-surgery and at follow up. Tumour tissue (fresh frozen) will be obtained at screening (Endoscopic ultrasound biopsy) and during surgery (intra-operative transduodenal tru-cut biopsy). At the time of surgery, tissue will be obtained from the resected tumour following pathological examination and prepared as fresh frozen and formalin fixed samples. Patients will be consented for the donation of a blood and biopsy sample at screening. The consent for the main trial will include all subsequent sample collection. The collection, processing, storage and shipment of samples will be carried out in accordance with ESPAC-5F standard operating procedures.

#### 8.5.1 Translational Blood Sample Collection

Translational bloods will be collected at the time of screening. For all patients randomised further translational bloods will be collected at specified time points throughout the trial as indicated in section 8.1, Schedules of Trial Procedures and as summarised in Table 20 below.

At each time point blood will be collected in one 10ml EDTA KE tube (BD Vacutainer) for plasma and cells and one 8ml Serum SST tube (BD Vacutainer) for serum. Bloods will be processed and stored locally at -80°C (subject to site facilities) until shipment to the central laboratories (University of Liverpool GCLP Facility) is arranged. Details of blood sample collection, processing and storage procedures are provided in SOP SSES5F001. Shipping procedures are provided in SOP SSES5F005.
<table>
<thead>
<tr>
<th>Trial Arm</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Sample</td>
<td>10ml EDTA 8ml Serum</td>
<td>10ml EDTA 8ml Serum</td>
<td>10ml EDTA 8ml Serum</td>
<td>10ml EDTA 8ml Serum</td>
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<tr>
<td>Total Samples</td>
<td>3</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Visit</td>
<td>• Screening • Post-surgery • Follow up 1</td>
<td>• Screening • Cycle 1 Day 8 • Cycle 1 Day 15 • Cycle 2 Day 15 • Re-stage • Post-surgery • Follow up 1</td>
<td>• Screening • Cycle 2 Day 1 • Cycle 3 Day 1 • Cycle 4 Day 1 • Re-stage • Post-surgery • Follow up 1</td>
<td>• Screening • Radiotherapy Week 2 Day 1 • Radiotherapy Week 4 Day 1 • Radiotherapy Week 6 Day 1 • Re-stage • Post-surgery • Follow up 1</td>
</tr>
</tbody>
</table>

**Arm B immune response subgroup** - a small number of patients randomised to Arm B of the trial will be invited to participate in the immune response sub study. This sub study will provide an evaluation of the immune system before neoadjuvant treatment, during and after neoadjuvant treatment and after surgery. For this subgroup of patients a sodium heparin blood draw, collected in two 6ml sodium heparin tubes (BD Vacutainer) will be taken at four time points throughout the trial (Randomisation, Cycle 1 Day 8, Re-stage and Post surgery visits), as indicated in section 8.1, Schedules of Trial Procedures. These samples will be taken in addition to the Arm B EDTA and serum blood draws. The immune response sub study is applicable to patients attending the Royal Liverpool University Hospital only.

### 8.5.2 Translational Tissue Sample Collection

Tissue samples for the translational study will be collected at the time points indicated in section 8.1, Schedules of Trial Procedures.

#### 8.5.2.1 Diagnostic Biopsy Samples at Screening

At screening patients will be consented for the donation of a biopsy tissue sample. This is not a compulsory part of the study however the tissue will be very important to the translational work. The sample will be taken during an Endoscopic Ultrasound. The sample must be placed immediately into Allprotect tissue reagent (supplied with the sampling kits) for stabilisation and then frozen. Samples will be stored locally at -80°C before shipment to the central laboratories is arranged. Details of the collection, processing and storage of EUS biopsy samples are provided in SOP SSES5F003. Shipping procedures are provided in SOP SSES5F005.

For patients undergoing a diagnostic biopsy, we ask that they are approached to provide a research sample at the same time as the diagnostic procedure, using the ESPAC-5F Pancreas Diagnostic Biopsy Research Sample Collection Patient Information Sheet and corresponding Informed Consent Form.

For patients already having undergone a diagnostic biopsy - we ask that they are approached to see if they will consent to undergo a further biopsy for the purpose of the trial. Patients should be approached using the ESPAC-5F Trial Research Samples Patient Information Sheet and corresponding Informed Consent Form.

#### 8.5.2.2 Intra-operative Biopsy and Samples

For all patients randomised at the time of any subsequent surgery and following appropriate consent, a tumour biopsy sample and samples of pancreatic juice will be taken. Patients will also be consented for permission to use tissue prepared from the resected tumour removed as a result of surgery. Details of the collection, processing and storage of tissue samples taken during and after surgery are provided in SOP SSES5F004. Shipping procedures are provided in SOP SSES5F005.
The samples required at the time of surgery are as listed below:

- Tumour biopsy sample (transduodenal pancreatic biopsy)
- Pancreatic juice (juice supernatant and cell pellet)
- Normal and tumour tissue specimens from the resected tumour (fresh frozen)
- Normal and tumour tissue specimens from the resected tumour (formalin fixed paraffin embedded tissue)

**Collection of tumour biopsy and pancreatic juice during surgery:**

A transduodenal tru-cut biopsy of the tumour will be collected during surgery; six tru-cut biopsies of the pancreas tumour will be taken, the cores must be placed immediately into Allprotect tissue reagent (supplied with the sampling kits) for stabilisation and then frozen. Samples will be stored locally at -80°C before shipment to the central laboratories is arranged. In addition a sample of the secretions from the pancreas (pancreatic juice) will be collected, processed and stored at -80°C in accordance with SOP S5ES5F004.

**Collection of frozen tissue and formalin fixed paraffin embedded tissue post resection:**

Following pathological examination of the resected tumour, normal and tumour tissue specimens will be taken, these samples must be placed immediately into Allprotect tissue reagent (supplied with the sampling kits) for stabilisation and frozen. Samples will be stored locally at -80°C before shipment to the central laboratories is arranged. Sections of the resected tumour (normal and tumour tissue specimens) will also be prepared in the pathology department as formalin fixed paraffin embedded (FFPE) tissue blocks.

### 8.6 Quality Assurance

#### 8.6.1 Radiology

Multidetector CT images will be transferred from the participating centre to the Radiology department at the Royal Liverpool and Broadgreen University Hospital Trust and will be identifiable by unique screening number only. There will be central radiology review under Dr Jonathan Evans to ensure that potential participants satisfy the criteria confirming borderline resectability.

Confirmation of borderline resectability will be made by the next available working day following receipt of CT scans, CRFs and the participating centre informed.

Potential participants failing to meet the criteria for borderline resectability at central review will not subsequently be eligible to participate in the trial.

The process to be followed for image and information exchange for Central Review is described in ESPAC-5F CENTRAL REVIEW WORK INSTRUCTION (Using IEP System) INS_D031.

For sites without access to the Image Exchange Portal (IEP) and for non-UK sites, CT images can be transferred electronically via secure server, accessible from the LCTU website (www.LCTU.org.uk). PLEASE NOTE: RANDOMISATION WILL TAKE LONGER TO COMPLETE WHILE WE WAIT TO RECEIVE THE CT SCANS IF SENT THROUGH THE POST FOR CENTRAL REVIEW.

Please refer to document ESPAC-5F CENTRAL REVIEW WORK INSTRUCTION (without IEP system) INS_D032.

In addition we will request the anonymised re-staging CT scan report at the same time point as the re-staging CRF.
8.6.2 Pathology

There will be a central pathology review for quality assurance. Central pathology review will be carried out under Professor Fiona Campbell, consultant Gastrointestinal Pathologist (Royal Liverpool and Broadgreen University Hospitals NHS Trust).

All diagnostic specimens and histology slides of resection specimens will be reviewed to confirm the local assessment.

In the event of a histological/cytological discrepancy being found on review, Professor Campbell will confer with the participating centre pathologist and the PI will be informed.

Histology/Cytology samples requested by the LCTU for central review will be sent to:

Professor Fiona Campbell
Consultant Gastrointestinal Pathologist
Department of Pathology
Royal Liverpool University Hospital
5th Floor Duncan Building
Daulby Street
Liverpool
L69 3GA

8.6.3 Radiotherapy

A separate detailed RT planning guidance will developed to supplement the RT section of the main protocol. RT workshops will be held during the course of the trial. Pre-trial evaluation of a test case and/or real-time review of contours will be required. Planning information will be collected prospectively through a planning assessment form (PAF). Further details of Pre-trial and On-trial RT Quality Assurance will available from the NCRI RTTQA website (www.rtttrialsqa.org.uk/).

8.6.4 Surgery

Eligible patients will undergo surgical exploration for resection. Minimum standards will apply – agreed by the surgical working party and incorporated into the ESPAC-5F Surgical Handbook (SSESSF_D031). All patients on arms A – D who undergo surgery will be required to take surgical photographs. We will also request the anonymised histology report at the same time point as the Surgery CRF.

8.7 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient’s usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient’s GP will be asked to provide follow-up information to the recruiting centre.

8.8 Trial Closure

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 the trial will be notified to the MHRA and MREC as required.

The trial is closed when the required number of events for the secondary endpoints, disease and local disease free survival rate and overall survival, as defined in section 9.3.2, is reached and the database has been fully cleaned and frozen for each of these two final analyses.
9  STATISTICAL CONSIDERATIONS

9.1  Introduction

A feasibility study is required since there are several questions to be answered before a full Phase III trial can be undertaken. Firstly, the feasibility of recruiting to a large Phase III trial has to be assessed. Secondly, some information on whether neoadjuvant therapy can improve survival over survival following immediate surgery is needed and if so, which therapy(ies) appear to be the best to be taken forward. Thirdly, the feasibility study is needed to better understand the balance of survival for the two separate groups:

(i) those patients that actually have resections, and
(ii) those patients for whom resection is not actually possible and how this differs for patients receiving neoadjuvant therapy and those who have immediate surgery.

There is the possibility that we will be faced with a difficult dilemma: it is possible that:

(i) neoadjuvant patients who are resected have superior survival prospects than the resected immediate surgery patients, but
(ii) the neoadjuvant patients who are not resected have inferior survival prospects than the immediate surgery patients who are not resected.

Hopefully, the feasibility study will shed some light on this. The inclusion of other arms may be possible if more effective agents become available.

9.2  Method of Randomisation

Central randomisation using a computer programme will be undertaken by the CR-UK Liverpool Cancer Trials Unit. Minimisation will be used for the allocation of treatments, incorporating a random element to prevent the chance predictability. Centre will be used as the sole stratification factor and due to centres collaborating to administer all four treatments, stratification will be by the amalgamated centres instead of individually.

There will be allocation concealment. The trial is open-labelled due to the different treatment modalities. Major factors which may affect outcomes are (i) the extent of vascular involvement and (ii) surgical variability between centres. Stratification by centre therefore will help to reduce bias. The effect of vascular involvement will be reviewed.

Data from the CRFs will be entered onto a MACRO4 database with extensive data validation checks alerting all missing data to be queried. Missing data will be monitored and strategies developed to minimise its occurrence. Central statistical data monitoring will summarise missing or inconsistent data periodically.

9.3  Outcome Measures
9.3.1 Primary

1. Recruitment rate.

Recruitment rate will be measured by (i) recruitment rate by centre (ii) overall recruitment rate and (iii) a graph comparing expected versus actual cumulative recruitment. The recruitment target is 100 patients in 39 months.

2. Resection rate.

An overall resection rate will be measured using the total number of patients at baseline. A second resection rate will also be measured using only the patients who undergo explorative surgery. R1 and R0 resection margins will be used when measuring the resection rate – R2 resection margins will be excluded.

9.3.2 Secondary

1. R0 resection margin rate.

An overall R0 resection rate will be measured using the total number of patients at baseline. A second resection rate will also be measured using only the patients who undergo explorative surgery. The R0 resection margin will be recorded according to the Royal College of Pathologists report on Standards and datasets for reporting cancers [47].

2. Toxicity.

Formal toxicity assessments will be performed at each study visit and graded according to the NCI-CTCAE v4. The proportion of patients experiencing grade 3/4 toxicity will be measured.

3. Postoperative complications.

Postoperative complications will be measured using morbidity and mortality rates. Postoperative morbidity will be recorded following surgery and classified according to existing guidelines. Postoperative mortality will be recorded as the 30 day mortality rate.

4. Response rate.

An overall response rate will be measured using the number of patients at baseline. Response will be assessed in accordance with RECIST 1.1 guidelines [41] (www.recist.com/files/Recist-1.1-Fanbook.pdf) and those patients achieving partial or complete response with disease control will be compared.

5. Disease and local disease free survival rate.

Disease and local disease free survival rate will be measured for the patients who undergo explorative surgery. Disease and local disease free survival are defined as the number of days between the date of surgery and disease or local disease recurrence, respectively.

6. Overall survival.

Overall survival will be recorded for all patients. Survival is defined as the number of days between date of randomisation and date of death due to any cause or the date of the last follow-up if the patient is still alive at the time of analysis.

7. Quality of life.
Quality of life will be assessed with the EORTC Quality of Life Questionnaire version 3. The questionnaires will be completed as per the Table of Assessments in Section 8 by all patients. The data will be scored according to the algorithm described in the EORTC scoring manual which linearly transforms the data from categorical scales to a score of 0-100.

### 9.4 Sample Size and recruitment

The aim is to recruit 40 patients to Arm A and 20 to each of Arms B, C and D. This is a feasibility study and is not powered to compare the resection rates for the different Arms with each other. However, the sample size is large enough to compare the resection rate of Arms B, C and D combined with that for Arm A, using a one-sided test ($n_1=40$, $n_2=60$, $p_1=0.35$, $p_2=0.55$, significance level = 0.2, power = 82% where $p_1$ and $p_2$ are the resection rates for Arm A and Arms B, C, D combined, respectively).

Initially, the trial was design for recruiting 100 patients over a 24 month period using 16 centres. It was estimated to open centres at a rate of 2 per month for 8 months. Six high volume centres were expected to be opened first and to recruit approximately 7 patients per year, followed by up to 10 medium volume centres that were expected to recruit approximately 4 patients per year. The overall expected recruitment was 10 patients by month 6, 30 patients by month 12, 65 patients by month 18 and 100 patients by month 24.

The initial recruitment projection has been reviewed during the course of the study due to difficulties in opening centres and randomising patients in the first months of the trial. In order to tackle the poor recruitment, more centres have been approached and the study period has been extended by 15 months. Therefore, the revised recruitment estimates are based on 24 centres, expected to recruit on average 2.6 patients per month over a period of 39 months. Bearing in mind that this is a feasibility study and it is not powered for comparisons between arms, 75 patients (30 for Arm A, 15 for Arm B, C and D) is considered the minimum number of patients needed to explore the other clinical questions of the study.

### 9.5 Interim analysis and stopping guidelines

No formal interim analysis will be performed during the course of the feasibility study. The ISDMC will assess the actual recruitment rates and makes decisions on whether to stop the trial based on poor recruitment.

### 9.6 Outline of analysis

Much of the analysis will be performed using summary statistics and graphics. Feasibility and overall recruitment rate will be assessed at the opened centres by producing recruitment graphs of the expected and observed cumulative recruitment. Furthermore, observed recruitment rates, by centre and overall, will be summarised along with a 95% confidence interval.

For the primary outcome resection rate Arm A will be compared with Arms B, C and D combined using a chi-squared or Fishers exact test. The secondary outcomes will be compared using a chi-squared or fishers exact test on a regimen basis.

Kaplan-Meier curves will be produced for disease free and overall survival times and tested using the log-rank test. Estimates will be made of the one year survival rate and, where possible, estimates of median survival times. Summary statistics and graphics will be used to analyse the quality of life scores from the EORTC models and longitudinal models fitted to compare arms; recognising that the small sample sizes will allow only large differences to become statistically significant.

Although these statistical tests will be carried out, the feasibility study is not powered to find small differences between arms. Analysis will be on an ITT basis.
Overall success would be based on evaluation of several criteria:

(i) One European site open and first patient recruited within 12 months.

(ii) Achieving the overall recruitment rate (100 patients in 39 months).

(iii) Evidence of at least one treatment deemed worthy of taking forward to a phase III study such as:

a. the overall resection rate in combined arms B, C and D being superior to that of arm A, or

b. superiority of one arm to control in a main secondary outcome measure (R0 resection margin rate, operative complication/mortality rate, response rate, survival) together with an acceptable toxicity/tolerability profile.

If success is met on all criteria, then a phase III study will be planned. If there is only partial success the trial procedures will be reviewed to determine whether improvement would be possible and a provisional phase III trial planned conditional on this.
10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6, they should be used when dealing with any adverse event occurring in patients on the ESPAC-5F trial

Adverse Event (AE)

Any untoward medical occurrence (i.e. any unfavourable or unintended sign, including abnormal laboratory results, symptom or disease) in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the trial Reference Safety Information for the Investigational Medicinal Product.

a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product
b) In the case of any other investigational medicinal product, in the investigator’s brochure relating to the trial in question.

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

Any adverse event or adverse reaction is classified as serious if it:

a) results in death
b) is life-threatening * (subject at immediate risk of death)
c) requires in-patient hospitalisation or prolongation of existing hospitalisation **
d) results in persistent or significant disability or incapacity, or
e) consists of a congenital anomaly or birth defect
f) other important medical events ***

* ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

*** Other 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 in the definition above should also be considered serious.
10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient’s condition

10.2.3 Reporting of Pregnancy

The trial will be conducted in accordance with information provided within the Summary of product characteristics of the trial Investigational Medicinal Products regarding contraception for both male and female participants.

If a patient or their partner becomes pregnant during treatment or in the six months following treatment, a completed Pregnancy Report Form must be faxed to the LCTU within 24 hours of learning of its occurrence. (Should you need a copy of the Pregnancy Report Form please contact the trial coordinator.) On pregnancy outcome, the final Pregnancy Report Form should be faxed to the LCTU 30 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome. Pregnancy outcomes should also be collected for the female partners of male patient participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form. The LCTU will report all pregnancies to the Trial Sponsor(s), MHRA and MREC.

Pregnancies must be reported by faxing a completed Pregnancy Report Form, sent within 24 hours of becoming aware of the event to the Liverpool Cancer Trials Unit
Fax. No: +44 (0) 151 794 8930

Pregnancy outcomes must be reported by faxing a completed final Pregnancy Report Form 30 days following the outcome to the Liverpool Cancer Trials Unit
10.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using CTCAE Version 4:

Table 21: Adverse Event General Grade Categories

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>Does not interfere with subject’s usual function (awareness or signs, but easily tolerated – acceptable)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Interferes to some extent with subjects usual function (enough discomfort to interfere with usual activity - disturbing)</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Interferes significantly with subjects usual function (incapacity to work or do usual activities – Unacceptable)</td>
</tr>
<tr>
<td>4</td>
<td>Life Threatening</td>
<td>Results in risk of death, organ damage, or permanent disability (unacceptable)</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>Results in death (unacceptable)</td>
</tr>
</tbody>
</table>

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 4, where applicable. [48].

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see Table 21 above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 22.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 22: Definitions of Causality

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Related</td>
<td>There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.</td>
</tr>
<tr>
<td>Unlikely</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment).</td>
</tr>
<tr>
<td>Possible</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>Probable</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>Highly Probable</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
</tbody>
</table>
An AE whose causal relationship to the study drug is assessed by the investigator as “possible”, “probable”, or “highly probable” is an Adverse Drug Reaction.

**Expectedness**

The Chief Investigator or delegated other will evaluate each SAE as to whether it is expected or not on behalf of the sponsoring organisations. The event is considered “unexpected” if the nature and severity of the event is not consistent with the current Reference Safety Information (RSI) (see section 10.6) for the medicinal product.

All events judged by the investigator to be related to the IMP, graded as serious and unexpected will be reported as a SUSAR.

**10.5 Reference Safety Information**

Each Investigational medicinal Product used within the remit of the ESPAC-5F trial protocol has an associated Reference Safety Information (RSI) document. RSI documents are reviewed and where required updated on an annual basis in line with the product of the sponsor Development Update Safety Report (DSUR) for each Product.

RSI is current for a year at a time as of the MHRA approval date for the trial. The RSI to be used for ESPAC-5F IMPs is taken from the following documents; however, please refer to the LCTU portal, www.LCTU.org.uk, for the current versions and dates of each RSI document:

**For Gemcitabine:**

Section 4.8 of the SmPC for Gemzar powder for solution for infusion (Gemcitabine) - Eli Lilly Company Ltd
www.medicines.org.uk/emc/medicine/596#UNDESIRABLE_EFFECTS

**For Capecitabine:**

Section 4.8 of the SmPC for Xeloda film coated tablets (Capecitabine) - Roche Products Limited
www.medicines.org.uk/emc/medicine/4619#UNDESIRABLE_EFFECTS

**For Fluorouracil:**

Section 4.8 of the SmPC for fluorouracil for injection/infusion – Accord Healthcare Ltd.
www.medicines.org.uk/emc/medicine/25800#UNDESIRABLE_EFFECTS

**For Folinic acid:**

Folinic acid generally administered as calcium or sodium folinate.

Section 4.8 of the SmPC for Sodiofolin solution for injection – medac GmBH
www.medicines.org.uk/emc/medicine/4363#UNDESIRABLE_EFFECTS

Section 4.8 of the SmPC for Calcium Folinate for injection – Hospira
www.medicines.org.uk/emc/medicine/8286#UNDESIRABLE_EFFECTS

**For Oxaliplatin:**

Section 4.8 of the SmPC for Oxaliplatin solution for infusion (oxaliplatin) – Sun Pharmaceuticals
http://www.medicines.org.uk/emc/medicine/27556#UNDESIRABLE_EFFECTS

**For Irinotecan:**

Section 4.8 of the SmPC for Irinotecan concentrate for solution for infusion – medac GmBH
www.medicines.org.uk/emc/medicine/22806#UNDESIRABLE EFFECTS

**NOTE:** The above documents are for the assessment of adverse events only. Management of the products should be conducted in accordance with the current SmPC for the brand of product being administered.
10.6 Reporting Procedures

All new (serious) adverse events should be reported from the start of pre-operative care (arm A patients) until 28 days after the operation and from the start of neo-adjuvant treatment (arm B-D patients) until 28 days following the last dose of neo-adjuvant treatment.

All SAEs that are related to surgery should be reported, however these will not be assessed as ‘unexpected’ and therefore will not be reported as SUSARs.

SAEs occurring in patients who have NOT received any trial treatment do not need to be reported

SAEs do NOT need to be reported during adjuvant treatment as this is standard care, not protocol-specific. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the LCTU in the first instance.

10.6.1 Non-serious ARs/AEs

All non-serious adverse events, whether expected or not should be recorded and updated at each study visit. They should also been followed in accordance with section 10.7. Adverse should be recorded either directly onto the patient AE form on the LCTU Pharmacovigilance MACRO database or on paper Case Report Forms. This will be discussed at site initiation and further instructions and training provided.

Each event should be recorded as a separate entry on the CRF or PV database. A change in grade should be treated as new event. For example: if a patient experiences/reports grade 1 nausea at the follow-up 1 visit and this increases to grade 2 at the follow-up 2 visit, two separate AE entries should be made closing out the first with the outcome ‘change in severity’.

10.6.2 Serious Adverse Events

Investigators MUST REPORT SERIOUS ADVERSE EVENTS (SAEs) WITHIN 24 HOURS of the local site becoming aware of the event. The SAE will be acknowledged by the LCTU within 2 hours of receipt by either fax or email.

The SAE form asks for the nature of the event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator/co-investigator should sign-off the causality of the event.

Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting. Sites are encouraged to use the LCTU online reporting system but where this is not possible paper reporting is acceptable.

The LCTU will further assess the event on behalf of the sponsor and notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines:

- fatal and life-threatening within 7 days of notification
- non-life threatening within 15 days.

All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research and Development Office.
Steps for reporting - USING PAPER SAE FORMS

i. The SAE form should be downloaded from the LCTU portal and completed by the responsible investigator i.e. the consultant named on the ‘signature list and delegation of responsibilities log’ who is responsible for the patient’s care.
   The investigator should assess the SAE for the likelihood that that it is a response to an investigational medicine.
   In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the LCTU immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the LCTU as soon as possible.
   The initial report shall be followed by detailed, written reports.

ii. Send the SAE form by fax (within 24 hours or next working day) to the LCTU.

   Fax Number: +44 (0) 151 794 8930

iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).

iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

v. Follow-up information is noted on another SAE form by ticking the box marked ‘follow-up’ and faxing to the LCTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.

vi. The patient must be identified by trial number, date of birth and initials only. The patient’s name should not be used on any correspondence.

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

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

- Research subject trial number and initials.
- Date of onset of event.
- Brief description of event and CTCAE (v4) grade.
- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name. Date of last administration of study drug.
- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name.
- Definition of serious

PLEASE ENSURE THAT MULTIPLE SERIOUS ADVERSE EVENTS ARE REPORTED SEPARATELY TO THE LCTU.
ONE SAE REPORT SHOULD ONLY RELATE TO ONE OVERALL DIAGNOSIS.
Acknowledgment of SAEs

Immediately upon receipt of an SAE (either via the online database or fax) the LCTU will send confirmation to site (by fax or e-mail). If no confirmation is received from the LCTU within 2 hours, site staff should contact the LCTU to confirm receipt of the original SAE.

10.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting AEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at death/ final follow-up; fatal; change in severity (non-serious AEs ONLY) or lost to follow-up/unknown.

10.8 Responsibilities

10.8.1 Principal Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the LCTU on an SAE form unless the SAE is specified in the protocol or Investigator Brochure as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

10.8.2 CR:UK LCTU

The LCTU is undertaking duties delegated by the trial co-sponsors, the University of Liverpool and the Royal Liverpool and Broadgreen University NHS Trust and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.

- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTU first becoming aware of the reaction.

- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;

- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
• New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:

  a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;

  b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;

  c. A major safety finding from a newly completed animal study (such as carcinogenicity).

  d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

• Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTU will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The LCTU will also send an annual safety report containing a list of all SARs to regulatory authorities and

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.
11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The ESPAC-5F trial will be conducted in accordance with, but not limited to, the Human Rights Act 1998, the DPA, Freedom of Information Act 2000 subject to the provisions of sections 41 and 43 thereof, the EU Clinical Trials Directive, the Medicines for Human Use (Clinical Trials) Regulations 2004, the Medicines Act 1968, the Human Tissue Act 2004, ICH GCP, the Declaration of Helsinki 1996 and the NHS Research Governance Framework for Health and Social Care, as amended from time to time.

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) and to allow a copy of their completed signed consent form to be sent to the Liverpool Cancer Trials Unit.

This study may be terminated at the request of the Chief Investigator, ISDMC, Independent Ethics Committee or the 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 of any new information related to the study drug as and when appropriate.

11.2 Ethical Approval

The trial protocol has received the favourable opinion of the NRES Committee North West - Haydock Multi-centre Research Ethics Committee (MREC) but all participating sites must undergo site specific assessment via the IRAS (Integrated Research Application System). A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to LCTU before patients are entered. The LCTU should receive notification of positive SSA for each new centre via the site’s R&D department.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual’s participation. Informed consent is required for all patients participating in LCTU coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient representative for their records and a copy placed in the medical records, with the original retained in the Investigator Site File. The patient may withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.
11.4 Study Discontinuation

The reason for discontinuation of study treatment/study should be clearly documented and the end of treatment and end of study CRFs completed.
12 REGULATORY APPROVAL

The ESPAC-5F trial received clinical trial authorisation (CTA) from the MHRA on 05/Mar/2014 (reference: 04196/0031/001-0001) and received approval from the North West – Haydock ethics committee on 18/Mar/2014 (reference: 14/NW/0036).

The trial has also been registered with EudraCT (reference: 2013-003932-56) and has an International Standard Randomised Controlled Trials Number (ISRCTN89500674).
13 TRIAL MONITORING

Site monitoring is conducted to ensure protection of patients participating in the trial, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements.

13.1 Risk Assessment

In accordance with the LCTU SOPs a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors
- Chief Investigator
- Trial Coordinator
- Trial Statistician
- LCTU Operational Director

In conducting this risk assessment, the contributors considered the risks associated with the trial IMP(s)/intervention(s) for the IMP(s)/intervention being investigated, risks related to the design and methods of the trial (including risks to participant, safety and rights, as well as reliability of results), organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is assigned according to the following categories:

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

This trial is considered to be a Type B = Somewhat higher than the risk of standard medical care.

13.2 Source Documents

Source Data

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

Source Documents

Original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial (ICH E6, 1.52). 62

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. Data recorded in the CRF should be consistent and verifiable with source data in source documents other than the CRF (e.g. medical record, laboratory reports and nurses’ notes). Each participating site should maintain appropriate medical and research records for this trial, in compliance with
ICH E6 GCP, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects.

For data where no prior record exists and which are recorded directly in the CRF (e.g. inclusion/exclusion criteria, adverse events and Quality of life questionnaires), the CRF will be considered the source document, unless otherwise indicated by the investigator.

In addition to the above, date(s) of conducting informed consent including date of provision of patient information, trial screening number, trial number, study treatment and the fact that the patient is participating in a clinical trial should be added to the patients’ medical record contemporaneously.

13.3 Data Capture Methods

Trial data will be captured using paper case report forms with the exception of adverse and serious adverse events, which will be captured electronically using the LCTU Pharmacovigilance system.

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”.

All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRF pages will be available for sites to download from the trial website, www.LCTU.org.uk.

13.4 Monitoring at LCTU

Data stored at LCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be returned to the local site by post or fax for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line and initialled (see section 13.3.1). The amended version should be returned to LCTU and the site’s copy should also be amended. LCTU will send reminders for any overdue and missing data.

13.5 Clinical Site Monitoring

13.5.1 Direct Access to Data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the patient’s confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Case report forms will be labelled with patient initials and unique study screening and/or study number. Multidetector CT images will be transferred to Dr Jonathan Evans the Radiology
department at the Royal Liverpool and will be identifiable by unique screening number only. Biopsy samples and paraffin blocks will be transferred to Dr Campbell in the department of pathology at the Royal Liverpool Hospital and will be identifiable by unique study number only.

Consent forms sent to the LCTU as part of the registration process may contain patient identifiers for the purpose of monitoring as described in the study risk assessment. Such information will be stored in secure, locked cabinets.

13.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The ESPAC-5F Investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsors site(s), Cancer Research UK (CR-UK) Liverpool Cancer Trials Unit or at any investigators 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.

13.6 Records Retention

The investigator at each investigational 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 the Sponsor or the LCTU 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.

The LCTU 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 the point where it is decided that the trial documentation is no longer required; the Investigator will be responsible for the destruction of all site trial specific documentation and the Sponsor/LCTU will be responsible for the destruction of all trial related materials retained by the Sponsor/LCTU.
14 INDEMNITY

ESPAC-5F is co-sponsored by the University of Liverpool and the Royal Liverpool and Broad green University Hospital NHS Trust and co-ordinated by the LCTU in the University of Liverpool.

The University of Liverpool and the Royal Liverpool and Broad green University Hospital NHS Trust does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity.

As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:

“A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process”.
15 FINANCIAL ARRANGEMENTS

This is a non-commercial trial, and no direct payments are available to cover the costs associated with patient recruitment, treatment administration, follow-up visits, data collection or reasonable travel expenses.

The trial is funded by Cancer Research UK, consequently having automatic endorsement from the National Cancer Research Network (NCRN) and UK Clinical Research Network (UKCRN). These organisations will be responsible for providing local investigators with the necessary research infrastructure.
16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Liverpool Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of at least an independent chairperson, and a biostatistician and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

16.3 Independent Safety and Data Monitoring Committee (ISDMC)

The independent Safety and Data Monitoring Committee (ISDMC) consists of an independent chairperson, plus 2 independent members an expert in the field of oncology, and an expert in medical statistics.

The ISDMC is responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC first convened on Thursday, 20th March 2014 and will then define the frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.
17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (www.icmje.org) will be respected.

All investigators who recruit patients will be named as co-authors. All participants will be included in any publications; order and ranking dependant as principle based on number of patients recruited. Everyone who collects tissue will be included in all publications.

All publications shall include a list of participants, and if there are named authors, these should include the trial’s Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and ISDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.
## 18 PROTOCOL AMENDMENTS

<table>
<thead>
<tr>
<th>Version</th>
<th>Summary of Changes</th>
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<tbody>
<tr>
<td>Protocol v1 20/12/2013</td>
<td>Original</td>
</tr>
<tr>
<td>Protocol v2 24/02/2014</td>
<td>1) Additional statement in section 5.2 following original MHRA review of version 1.  2) Additional statement in section 10.2.3 following original MHRA review of version 1.</td>
</tr>
<tr>
<td>Protocol v3 05/08/2014</td>
<td>1) Updated numbering of tables.  2) Contact details updated.  3) Inclusion criteria no. 8 modified from creatinine clearance to glomerular filtration rate.  4) Exclusion criteria no. 4 to allow exceptions case by case, e.g. methotrexate for rheumatoid arthritis.  5) Section 4: two additional procedures for the screening and randomisation process.  6) Section 7.3.1: allow concentrate for solution for infusion as well as powder, as gemcitabine is now generic.  7) Section 7: clarification that there is a 2-day window for taking toxicity-assessment bloods.  8) Section 7: clarification regarding the use of G-CSF.  9) Section 7: clarification on managing patients with angina or angina-like pain.  10) Section 7.3.2: clarification of dose banding procedures.  11) Section 7.4.1, Arm C, FOLFIRINOX: folic acid may now be either calcium or sodium folinate rather than Sodiofolin as previously specified.  12) Section 7.4.2, Arm C, FOLFIRINOX: folic acid administration changed from 400mg/m² to local practice.  13) Section 7.5, Chemoradiotherapy: re-written for improved clarity and with more detail.  14) Section 8.1: addition of pathology central core lab review to the schedules of procedures and other clarifications.  15) Section 8.5, Translational study: re-written for clarity and to reflect laboratory SOPs.  16) Section 8.6, Quality Assurance: further information added regarding the transfer of radiology images to the LCTU; radiotherapy paragraph also added.  17) Section 9.2: minimisation specified as the method of randomisation.  18) Section 12: regulatory approval details added.  19) Section 17: additional information regarding the publication policy.  20) Miscellaneous administrative changes.</td>
</tr>
<tr>
<td>Protocol v4 28/04/2015</td>
<td>1) Updated numbering of tables.  2) Contact details updated.  3) Exclusion Criteria No 2 modified to Previous or concurrent malignancy diagnoses, except: i) curatively-treated basal cell carcinoma of skin, ii) carcinoma in situ of cervix, iii) previous cancers treated with curative intent, ending treatment ≥ 5 years ago.  4) Exclusion Criteria No 4 modified to Previous chemotherapy ending &lt; 5 years ago (exceptions may be given case by case by the CI, such as methotrexate for rheumatoid arthritis).  5) Schematic of Study Design modified to show Review of staging MDCT scan by central laboratory will be included within the screening process.  6) Section 7.3.3 Dose Modifications: Information on treatment delays has been added to this section: 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.  7) Section 7.4.1 Active Ingredient Name /Dose for 5-Fluorouracil modified typo to show correct 50 mg fluorouracil in 10 ml solution not 500mg.  8) Section 7.4.1 Irinotecan formulation modified to show Concentrate For Solution For Infusion not injection as per the approved SmPC for Irinotecan.</td>
</tr>
</tbody>
</table>
9) Section 7.4.3 Dose Modifications Information on treatment delays has been added to this section: 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.

10) Section 7.5.2 Optional Pre-Radiotherapy Investigations. Reworked to allow local standard of care using additional diagnostic assessments, as per institutional practice, may be of assistance in identifying disease not visible on CT and distinguishing pancreatic tumour from duodenum, but GTV defined by diagnostic CT scan must not be reduced based on these optional investigations alone.

11) Table 15 Medical abbreviation BD (Bis Die) added to Capecitabine column to show dose is twice daily.

12) Section 8.1 Schedules of Trial Procedures: Screening and baseline procedures given more time between screening and randomisation. Neurological examination is only required during treatment in Arms B and Arm D if clinically indicated and as per local standard practice.

13) Section 8.1 Table 19 Chemoradiotherapy: Typo WHO performance status was identified in both columns of Screening and Baseline. It is only required in column 1 at -4 weeks.

14) Section 8.5.1 Translational Blood Sample Collection. We ask sites to store blood samples locally at ~80°C. We have added (subject to site facilities) this will allow sites to follow the updated SOP SSES5F005 blood sample collection, processing and storage procedures where other temperatures will be acceptable depending on local site facilities determined on a site by site basis.

15) Section 8.6.1 Radiology: deleted the term images can be posted to the LCTU as we will be accepting image transfers only.

16) Section 10.5 Reference Safety Information has been updated to show new SmPC to be used as a safety reference for Oxaliplatin.

17) Section 10.6.2 Serious Adverse Events: minimum dataset required added the word dated to requirement of signature of investigator/co-investigator and clearly printed name.

### Protocol v5 27/01/2016

1. **Trial contact details updated**
2. **Inclusion criteria point 3 amended to allow uncovered metal stents** – also updated in the schedule of trial assessments.
3. **Exclusion criteria points 2 and 4 amended from 5 years to 3 years.**
4. **Exclusion criteria 2 amended to include carcinoma in situ of breast; bladder**
5. **Adjuvant treatment amendment throughout protocol and trial schematic design to allow adjuvant therapy to be as per physician’s choice.**
6. **Table 7: The sentence copied from Hepatic Impairment section to above table 7 for clarity. ‘Haematological toxicity due to capecitabine is rare. Where haematological toxicity is encountered, the guidance in Table 7 should be followed’.**
7. **The risk section 13.1 has been updated in line with the ESPAC-5F risk assessment and now shows the MHRA stratification approach into type A, B or C.**
8. **Quality Assurance section 8.6 Protocol**

   We would like to collect anonymised CT scan report when we collect the re-staging CRF.
   We would like to collect the histology report when we collect the surgery CRF.
REFERENCES


47. https://www.rcpath.org/UKrdonlyres/954273A2-3F01-4897-B0F6-C136231DF65F/0/datasethistopathologicalreportingcarcinomasmay10.pdf