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PET-PANC

CONFIDENTIAL

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Glossary			
AC	Attenuation Corrected	MDCT	Multidetector Computerised Tomography
AE	Adverse Event	MDT	Multidisciplinary Team Meeting
AR	Adverse Reaction	MREC	Main Research and Ethics Committee
ARSAC	Administration of Radioactive Substances Advisory Board	MRI	Magnetic Resonance Imaging
CA 19-9	Carbohydrate antigen 19-9	NHS	National Health Service
CEACS	Cost Effectiveness Acceptability Curve	NOPR	National Oncologic PET Registry
CI	Chief Investigator	NRES	National Research Ethics Committee
CRB	Criminal Records Bureau	OSEM	Ordered Subsets Expectation Maximisation
CRF	Case Report Forms	PACS	Picture Archiving and Communication System
CRP	C-Reactive Protein	PET NAC	PET Non Attenuation Corrected
CSRI	Client Service Receipt Inventory	PET/CT	Positron Emission Tomography / Computerised Tomography
CTRC	Clinical Trial Research Centre	PI	Principal Investigator
CTU	Clinical Trials Unit	PIC	Patient Informed Consent
CV	Curriculum Vitae	PIS	Patient Information Sheet
DICOM	Digital Imaging & Communication in Medicine	PTC	Percutaneous Transhepatic Cholangiography
DM	Data Manager	pTNM	Pathology Tumour Node Metastasis
DMS	Document Management System	QA	Quality Assurance
ERCP	Endoscopic Retrograde Pancreatography	QC	Quality Control
EUS	Endoscopic Ultrasound	R&D	Research and Development
FBC	Full Blood Count	SAE	Serious Adverse Event
FDG	F-2-Fluro-2-Deoxy-D Glucose	SAR	Serious Adverse Reaction
FLT	F-Flurothymidine	SC	Study Coordinator
FNA	Fine Needle Aspiration	SSA	Site Specific Assessment
GCP	Good Clinical Practice	SUSAR	Suspected Unexpected Serious Adverse Reaction
GEE	Generalised Estimating Equation	SUV	Standard Uptake Value
GP	General Practitioner	TC	Trial Coordinator
HTA	Heath Technology Assessment	TMG	Trial Management Group
ICF	Informed Consent Form	TSC	Trial Steering Committee
ICH	International Conference on Harmonisation	U&E'S	Urea and Electrolytes
ISDMC	Independent Safety and Data Monitoring Committee	UAR	Unexpected Adverse Reaction
IRAS	Integrated Research Application System	UICC TNM	International Union Against Cancer TNM classification of malignant tumours
LCTU	Liverpool Cancer Trials Unit	USS	Ultrasound Scan
LFT	Liver Function Test	WCBA	Women of Child Bearing Age
LREC	Local Research Ethics Committee	WHO	World Health Organisation
MARS	Medicines Administration of Radioactive Substances		

1. Study Protocol Approval

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

Signature: _____ **Date:** _____

Professor Paula Ghaneh– Chief Investigator
Professor of Surgery
Department of Molecular and Clinical Cancer Medicine
University of Liverpool
Liverpool
L69 3GA

Signature: _____ **Date:** _____

Signed on behalf of the University of Liverpool (Co-Sponsor)
Professor Ian Greer
Executive Pro-vice Chancellor
Dean of the Faculty of Health and Life Sciences
University of Liverpool
Liverpool
L69 3GL

Signature: _____ **Date:** _____

Signed on behalf of the Royal Liverpool and Broadgreen University Hospitals NHS Trust (Co-Sponsor)
Professor Tom Walley
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Research and Development
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This protocol has been approved by:

- The Chief Investigator
- The Trial Management Group

2. Protocol Statements

2.1. General Information

This document describes the PET-PANC study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the assessment and 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 study, 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 study should be referred to the relevant Chief Investigator via LCTU.

2.2. 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, the Medicines (Administration of Radioactive Substances) Regulations 1978 ('MARS') and the LCTU Standard Operating Procedures

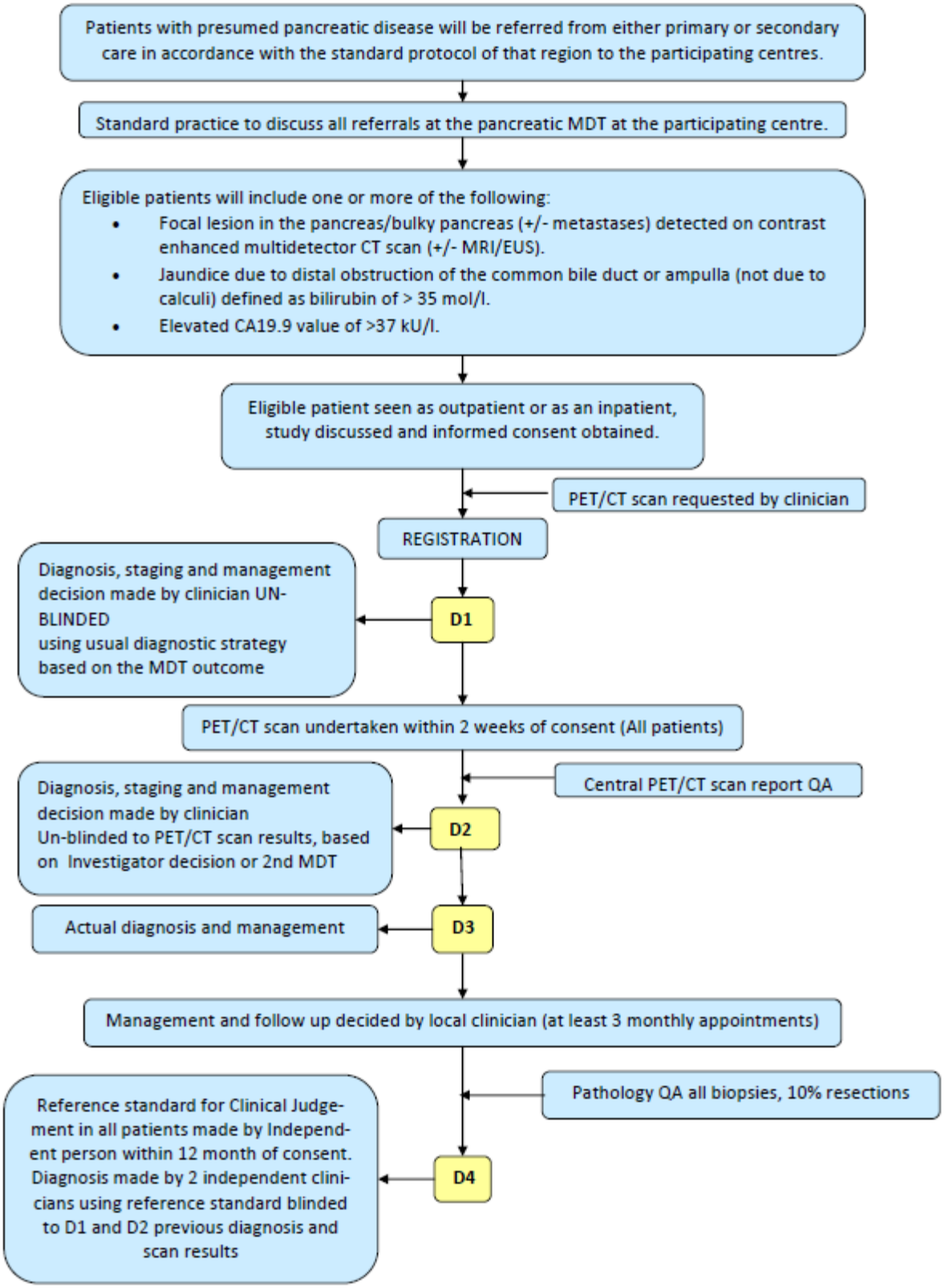
2.3. UK registration

This study will have National Research Ethics Service (NRES) approval and each centre must also undergo Site Specific Assessment by the relevant Trust Research and Development department and NHS sites must be granted Research and Development Approval from each Trust where the study will be carried out. In addition an ARSAC (Administration of Radioactive Substances Advisory Committee) research certificate must be obtained for all participating centres prior to recruitment of patients.

3. Protocol Summary

Title:	The impact of combined modality positron emission tomography with computerised tomography scanning (PET/CT) in the diagnosis and management of pancreatic cancer.
Phase:	Prospective diagnosis accuracy study
Sample Size:	Sample size set at 500 patients from the UK, following result of interim analysis
Study Period:	36 months
Main Inclusion Criteria:	1. Patients with suspected pancreatic malignancy as defined by one or more of; a. Focal lesion in the pancreas/bulky pancreas/dilated pancreatic duct (+/- metastases) detected on Multidetector CT scan (+/- MRI/EUS/USS) b. Jaundice due to distal obstruction of the common bile duct or ampulla (not due to calculi) defined as serum bilirubin. 35 µmol/l c. Serum CA19.9 value above 37KU/l 2. Able to attend for PET/CT scan. 3. Able to undergo Multidetector CT scan 4. Able to attend for up to 12 months follow-up 5. Fully informed written consent given.
Main Exclusion Criteria:	1. Patients younger than 18 years 2. Pregnancy 3. Patients with poorly controlled diabetes
Number of Sites:	Up to 30 major UK pancreatic tertiary referral units
Study Duration:	12 months per patient
Description of Intervention:	Combined modality positron emission tomography with computerised tomography scanning (PET/CT)
Primary Objective:	To determine the incremental diagnostic accuracy and impact of PET/CT in addition to standard diagnostic workup in patients with suspected pancreatic cancer
Secondary Objective :	1. To evaluate changes in diagnosis, staging, and associated intended patient management through the addition of PET/CT 2. To determine cost effectiveness of the addition of PET/CT in the diagnosis, staging and management of pancreatic cancer. 3. To evaluate the impact of the addition of PET/CT in differentiating pancreatic malignancy from chronic pancreatitis. 4. To identify which groups of patients would most benefit from PET/CT. 5. To report the incremental diagnostic value of PET/CT for particular types of pancreatic tumour.

Schematic of Study Design:



4. Background Information

4.1. Introduction

Pancreatic cancer is one of the major causes of cancer death. In the UK in 2005 the incidence of pancreatic cancer was 7,632 and the mortality in 2006 was 7,315 [1]. Over the past three decades there has been considerable progress towards understanding the biology of pancreatic cancer, refining imaging systems, improving surgical outcomes and more recently a focus on biomarkers to enable targeted therapies. In spite of these advances the overall survival figures for pancreatic cancer remain bleak. The five year survival rate for all patients with pancreatic cancer persists at less than 5% [2,3]. Most patients present with advanced disease due to late presentation and difficulties in early diagnosis. Median survival for patients with advanced disease is between 3-6 months, this can be improved with systemic chemotherapy [4]. The outlook for those patients who can undergo surgical resection is better. In specialised centres, resection rates of above 15% can be achieved [5]. Although surgery cannot guarantee a cure, the five year survival does improve to 10-15% following resection [6,7] and increases to 20-30% with adjuvant chemotherapy [8]. The pattern of disease recurrence following resection includes both locoregional failure and distant metastases [9]. The biggest risk factors for pancreatic cancer are increasing age, smoking, new onset diabetes mellitus, increased body mass index, chronic pancreatitis, hereditary pancreatitis and an inherited predisposition for pancreatic cancer (the latter may account for 10% of observed cases). Tobacco smoking is associated with a two-fold increase and because of the prevalence may account for around 30% of all cases with pancreatic ductal adenocarcinoma. Chronic pancreatitis is associated with a 15–25-fold risk [10].

4.2. Standard diagnostic practice

The diagnosis of pancreatic cancer can be challenging. Patients with pancreatic cancer may be relatively asymptomatic during its early course, with vague presenting symptoms such as back and epigastric pain. Until the systemic symptoms of weight loss, anorexia and obstructive jaundice appear; it can be a difficult diagnosis to achieve. The role of imaging in such patients is to identify a pancreatic lesion, determine its malignant potential, and assess its resectability. At the same time, it must also correctly identify inoperable carcinomas so that patients can receive appropriate therapy as soon as possible and be spared unnecessary operations. Standard diagnostic practice (along with tumour marker CA19.9 estimation) currently consists of:

1. Contrast enhanced multidetector computerised tomography (MDCT) (perhaps following an initial transabdominal ultrasound scan).
2. Endoluminal ultrasound (EUS) may be employed in cases where further information is required. Histology may be also obtained.
3. Therapeutic endoscopic retrograde pancreatography (ERCP) (or percutaneous transhepatic cholangiography-PTC) is used to relieve jaundice and obtain cytological brushings.
4. Laparoscopy and laparoscopic ultrasound may be used on a selective basis to stage a radiologically resectable tumour.

Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used marker in everyday practice. CA19-9 has a sensitivity of 70–90% and specificity of 90% [11]. False positive results are obtained in benign obstructive jaundice, chronic pancreatitis, cholangitis, cirrhosis, and ascites. CA19-9 is most useful in assessing response to treatment in advanced cases, identifying early recurrence in resected cases [12-14]. Elevated CA19.9 levels in patients with non-specific abdominal pain may be associated with a diagnosis of pancreatic cancer in 14% of cases [15].

Initial imaging may include transabdominal ultrasound [16] but the gold standard for pancreatic imaging is multidetector computed tomography. This technology provides three-dimensional multiplanar reconstruction techniques enabling accurate determination of tumour involvement of the common bile duct, pancreatic duct, and peripancreatic vasculature. Sensitivity and specificity of multidetector CT in detecting pancreatic malignancy is typically 97% and 72% respectively [17]. The positive predictive value for predicting unresectability (89%-100%) is high but the positive predictive value of CT for predicting

resectability (45%-79%) is low [18,19]. Pancreatic carcinoma typically manifests as a hypoattenuating focal mass relative to the enhancing pancreatic parenchyma on contrast-enhanced CT. However, approximately 11% of carcinomas are isoattenuating with the pancreas and their detection relies on secondary signs such as interruption of the pancreatic duct, distal pancreatic atrophy, and mass effect [20]. Chronic pancreatitis can show many of the features of adenocarcinoma on CT imaging, including having the appearance of a focal mass, appearing isodense or hypodense to the pancreatic parenchyma, pancreatic duct dilatation, and pancreatic atrophy. This can lead to up to 10% of pancreatic resections being performed for benign disease [21]. Limitations of CT also include small tumours and a diffusely enlarged or bulky pancreas. Bulky/diffuse enlargement on CT may be associated with malignancy in 8.7% of cases [22]. Furthermore, the sensitivity of CT for small hepatic and peritoneal metastases is also limited [18]. Magnetic resonance imaging can be helpful as an adjunct to CT, particularly for evaluation of small hepatic lesions that cannot be fully characterized by CT [23].

EUS is employed to visualise the whole pancreas, the related vasculature and associated lymph nodes and allows for EUS-guided FNA of pancreatic lesions and suspicious lymph nodes. EUS can be superior to multidetector CT at detecting and determining the T stage of pancreatic tumours with a sensitivity of 98% versus 86% respectively [24,25]. FNA with EUS is usually indicated when there is bulky pancreatic head or if there is diagnostic uncertainty if the lesion is inflammatory or malignant [26]. The sensitivity and specificity of EUS and FNA in detecting pancreatic cancer are 85%-90% and 95% respectively [27]. ERCP is used therapeutically to relieve obstructive jaundice and obtain cytological brushings [28]. Percutaneous biopsy is reserved only for patients with unresectable disease. Essentially, pancreatic biopsy (EUS or percutaneous) should not be performed on patients with resectable disease because of the risks of seeding, a false negative rate, complication rate and poor accuracy in cystic tumours, chronic pancreatitis and autoimmune pancreatitis [29]. Selective laparoscopy and laparoscopic ultrasound in patients with radiological resectable disease using serum CA19.9 and platelet lymphocyte ratio effectively increases resection rates and decreases unnecessary laparotomies [30,31].

4.3. FDG-PET in pancreatic cancer

Positron emission tomography (PET) is a functional imaging technology which enables visualisation, characterisation and quantification of biological processes in vivo. By using positron emitting radiotracers, PET provides unique information about the molecular and metabolic changes associated with disease. Glucose metabolism is often increased in malignant tumours resulting in increased cellular uptake of the glucose analogue ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG). Imaging the metabolic activity of tumours provides sensitive and specific information about the extent of disease. PET scanning images the whole body and therefore maybe helpful in looking for metastases. The extent to which PET may influence diagnosis and management in solid tumours has been assessed in a recent large cohort study by the National Oncologic PET Registry (NOPR) looked at 22,975 cases from 1178 centres. These patients had FDG-PET scans for a diagnosis of suspected cancer, cancer staging, restaging and suspected recurrence. Prostate, pancreatic and ovarian cancers represented 30% of cases. The post-PET plan was three fold more likely to lead to treatment than non-treatment (28.3% vs 8.2% OR=3.4 95% CI 3.2-3.6). Overall intended management was changed in 36.5% (95% CI 35.6-37.2) of cases [32]. FDG-PET scanning has been assessed pancreatic cancer. Studies have varied in evaluating the accuracy of FDG-PET in pancreatic carcinoma, however its usefulness at reporting early lesions remains unclear [33]. We assessed the role of PET in 112 patients with suspected pancreatic cancer [34], our study demonstrated sensitivity and specificity for FDG-PET of 73% and 60% and for CT of 89% and 65%. We found that FDG-PET had a similar accuracy to CT but did not provide any additional information in patients with equivocal CT findings. Pancreatic cancer is associated with a marked desmoplastic response and stromal inflammatory cells in and around the neoplasm may be responsible for 24% of the uptake of FDG. In our study 10 of the 12 patients with false-positive results had chronic pancreatitis. A meta-analysis compared FDG-PET with CT in studies of patients with pancreatic cancer [35]. Sensitivity and specificity for CT were 81% (95% CI 72-88%) and 66% (95%CI 53-77%) respectively. The addition of PET to positive CT resulted in sensitivity and specificity of 92% (95%CI 87-95%) and 68% (95% CI 51-81%). These results demonstrate

that the role for the addition of FDG-PET in the diagnostic work up of these patients remains to be proven and cannot be recommended as standard practice.

4.4. PET/CT in pancreatic cancer

Combined positron emission tomography and computed tomography (PET/CT) has been developed to add precise anatomic localization to functional data [36]. PET and CT is acquired concurrently and co-registered, merging functional information from PET with the anatomical information from CT. Several studies have demonstrated that FDG PET/CT is more accurate than FDG-PET [33,37] in solid tumours, including pancreatic tumours. In pancreatic cancer, a study by Heinrich et al [38] found that FDG PET/CT had a sensitivity of 89% for the detection of pancreatic cancer, altered treatment planning in 16% of 59 patients and was cost saving. A recent study [39] demonstrated that the sensitivity and specificity of FDG PET/CT was 88% and 89% respectively in patients being assessed for pancreatic cancer and changed the management of 6 (11%) patients. These patients were found to have extra-pancreatic disease which prevented them from undergoing pancreatic resection. Another study assessed two groups of patients; a diagnosis and staging group and a screening group for progressive or recurrent disease. The accuracy rate for FDG PET/CT for diagnosis and staging was 91.2% and 85.3% respectively. In the restaging group FDG PET/CT had a sensitivity of 90% [33]. The additional feature of PET/CT is semi-quantitative analysis of glucose uptake (FDG activity) in suspicious pancreatic lesions. Determination of FDG activity is obtained by calculating standardised uptake value (SUV) in a given region of interest. An SUV of >3.5 may indicate pancreatic malignancy; a recent study revealed SUV_{max} in malignant lesions of 6.5 +/-4.6 and 4.2+/-1.5 in benign lesions [40]. A definite cut off value is difficult to define for pancreatic malignancies and therefore qualitative data should also be included such as FDG tracer uptake patterns in clinical studies [40]. The use of contrast enhanced PET/CT may represent a complete diagnostic staging procedure without the need for a separate multidetector CT scan. It has been assessed in two recent studies. One found that contrast enhanced FDG PET/CT was superior to FDG-PET (p=0.035) and there was a trend (p=0.07) for contrast enhanced FDG PET/CT to be superior to unenhanced PET/CT [41] in assessing resectability. Another study assessed 46 patients with solid pancreatic lesions, the sensitivity and specificity of contrast enhanced PET/CT to detect malignancy was 89% and 74% [40]. The use of other radiopharmaceuticals such as ^{18}F-fluorothymidine (FLT) may be a focus for future investigations. FLT PET assesses the proportion of cells undergoing active proliferation and this process occurs before a change in glucose metabolism. This may be useful in monitoring response to therapy. In a pilot study of five patients with pancreatic adenocarcinoma, who underwent FLT PET/CT, FDG PET/CT and contrast enhanced CT; FLT PET/CT demonstrated poor lesion detectability [42].

4.5. Study Rationale

The diagnosis of pancreatic cancer has improved with the use of multidetector CT, EUS, ERCP and additional use of MRI. There are, however, up to 10-20% of patients in whom an accurate diagnosis is difficult. This proportion is increasing due in part to larger numbers of asymptomatic patients undergoing cross sectional imaging [43]. Invasive methods of diagnosis such as EUS +/- FNA can add to the accuracy of multidetector CT but may require an in-patient stay and have a recognised complication rate (1-2%) [44]. Currently patients with chronic pancreatitis, autoimmune pancreatitis, cystic lesions, small tumours <2cm, a bulky or diffusely enlarged pancreas on CT, a dilated pancreatic duct and no mass on CT, small volume metastatic disease and suspected recurrent disease (with no mass on CT) following resection are the most challenging patients to diagnose. A major goal of accurate diagnosis and staging is to avoid major pancreatic resection in patients who will not benefit; about 10-15% of patients who have a pancreatic resection have benign disease on final histology [21] and up to 20% of patients will develop recurrent disease 3-6 months post resection [45]. The use of a functional imaging technique such as PET/CT may add to staging of pancreatic cancer by diagnosing small volume metastatic disease and differentiate between benign and malignant lesions; it is vital that a well designed prospective study answers this question. Earlier diagnosis of pancreatic cancer will lead to a better prognosis for patients and PET/CT may be able to identify small volume disease or cancer arising in patients with chronic pancreatitis. There have been a number of studies to address diagnostic accuracy of PET/CT and two

have looked at the issue of changes in management due to PET/CT. The main drawbacks of previous PET/CT studies tend to be that these are single centre studies with small numbers of patients and difficulties in standardising PET/CT protocol in pancreatic cancer. For example one study focussed on patients undergoing neoadjuvant therapy [38] (therefore not widely applicable) and another was a retrospective review [39]. This prospective multicentre study aims to address these issues in a large group of patients to identify whether there is a role for PET/CT in addition to standard diagnostic work up in pancreatic cancer.

4.6. Potential Risks and Benefits

This study will assess the effects of adding PET/CT to the usual standard of care for patients with suspected pancreatic cancer. The main risks will be of the PET/CT itself and any possible delay to the patients diagnostic and management pathway. The risks of PET/CT scan are related to the radiotracer ^{18}F –FDG itself, allergic reaction to the radiotracer and radiation exposure from the CT scan. Allergic reactions to radiopharmaceuticals may occur but are extremely rare and are usually mild. The doses of radiotracer administered are small typically 8mSv for adults using 400MBq. The radiation dose from the CT scan can be low (e.g. an effective dose of about 7mSv) The risk of increased carcinogenesis associated with radiation exposure is outweighed by the benefits of correctly identifying patients who will can undergo surgery and also preventing unnecessary surgery in others. The scans will be performed in a timely manner to minimize any delay.

5. Selection of Centres/Clinicians

The study will be carried out in major pancreatic centres with annual referrals of over 100 pancreatic patients per year.

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

- Being a major pancreatic centre with annual referrals of over 100 pancreatic patients per year
- Conduct of pancreatic/hepatobiliary Multidisciplinary Team (MDT) meetings consisting of surgeons, gastroenterologists, radiologists, oncologists and pathologists.
- A lead clinician with a specific interest in, and responsibility for, supervising and managing patients with pancreatic disease
- Having a radiologist to act as co-investigator who is ARSAC registered
- Showing enthusiasm to participate in the study.
- Ensuring that sufficient time, staff and adequate facilities are available for the study.
- Providing information to all supporting staff members involved with the study or with other elements of the patients management.
- Access to a PET/CT scanner and the ability and willingness to send scans for central review.
- 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.

5.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) by local Research and Development (R&D) Department
b. Signed Research Site Agreement
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 International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
f. CV including a record of ICH GCP training – Other personnel on the delegation log
g. Clinical Study Protocol Receipt Form
h. Local laboratory accreditation/Quality Check
i. Local laboratory reference ranges
j. Provision of Patient information sheet, consent form and GP letter on trust headed paper
k. Completion of PET/CT test case to the satisfaction of the Core Pet/CT Lab
l. Ability to send multidetector CT scans, PET/CT scans and pathology samples for QA review.

5.2 Centre/Clinician Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the study.

6. Study Design

This is a multi-centre prospective diagnostic accuracy and clinical value study of PET/CT in suspected pancreatic malignancy.

6.1. Primary Endpoint

To determine the incremental diagnostic accuracy and impact of PET/CT in addition to standard diagnostic workup in patients with suspected pancreatic cancer.

6.2. Secondary Endpoint(s)

1. To evaluate changes in diagnosis, staging and associated intended patient management through the addition of PET/CT.
2. To determine cost effectiveness of the addition of PET/CT in the diagnosis, staging and management of pancreatic cancer.
3. To evaluate the impact of the addition of PET/CT in differentiating pancreatic malignancy from chronic pancreatitis.
4. To identify which groups of patients would most benefit from PET/CT.
5. To report the incremental diagnostic value of PET/CT for particular types of pancreatic tumour.

6.3. Study Intervention

Combined modality positron emission tomography with computerised tomography scanning FDG PET/CT will be used. Positron Emission Tomography (PET) scanning is now a widely accepted method for diagnosis of several types of cancer. Patients are given an injection containing a very short-lived (110-minute half life) radioactive form of glucose (^{18}F-labelled fluoro-deoxyglucose or FDG). The patient rests, typically for one to one and a half hours, while the FDG is metabolised in the body. We exploit the tendency of cancer cells to take up and use glucose much more than normal tissues and PET show cancers as foci of increased FDG uptake. The method is very sensitive (only trace amounts of FDG need be injected). Although these 'molecular images' provide important functional information, anatomical localisation of abnormal foci can be a challenge because of the limited anatomical detail with PET. Combined computed tomography (CT) PET scanners provide fused PET and CT images and has been shown to improve the diagnostic value of FDG imaging. A strict PET/CT study QA compliance document will be supplied to ensure efficacy of data from different sites.

6.4. Target Conditions

The analyses of test accuracy and staging will consider the following target conditions:

a) Pancreatic cancer (for the primary objective)
b) Stage of pancreatic cancer (UICC TNM classification as above for resectable, borderline resectable and unresectable disease)
c) Chronic pancreatitis
d) Particular types of pancreatic tumour.

7. Study Population

All patients are expected to be identified via the MDT meetings, which are standard practice for dealing with suspected cancer cases regardless of how each patient was initially referred to the hospital.

7.1. Inclusion Criteria

1. Patients with suspected pancreatic malignancy as defined by one or more of;
    a) Focal lesion in the pancreas/bulky pancreas/dilated pancreatic duct (+/- metastases) detected on Multidetector CT scan (+/- MRI/EUS/USS)
    b) Jaundice due to distal obstruction of the common bile duct or ampulla (not due to calculi) defined as serum bilirubin. 35 µmol/l
    c) Serum CA19.9 value above 37KU/l
2. Able to attend for PET/CT scan
3. Able to undergo Multidetector CT scan
4. Able to attend for up to 12 months follow-up
5. Fully informed written consent given.

7.2. Exclusion Criteria

1. Patients younger than 18 years
2. Pregnancy
3. Patients with poorly controlled diabetes

7.3. Patient Withdrawal from Study Intervention

In consenting to the study, patients are consenting to all study procedures, follow-up, and data collection. If voluntary withdrawal from intervention 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.

Patients may be withdrawn from the study for any of the following reasons:

a. Patient/Legal representative withdraws consent.
b. Intercurrent illness preventing further follow-up
c. Any change in the patient's condition that justifies the withdrawal of the patient in the clinician's opinion.

If a patient wishes to withdraw from the study, centres should nevertheless explain the importance of remaining on study follow-up, or failing this, of allowing routine follow-up data to be used for study purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (section 7.5).

7.4. Patient Transfer

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating study centre and for this study 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.

7.5. Withdrawal from Study Completely

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

7.6. Loss to Follow-up

If any of the study patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the study 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.

7.7. Co-enrolment Guidelines

Patients registered for the PET-PANC study are not restricted to entry onto any other clinical trials, studies or research projects. However information regarding any trial participation will be collected on the follow-up CRF forms.

8. Screening And Registration

8.1. Screening

Screening and Identification of eligible patients will take place at the research site's pancreatic MDT meeting typically consisting of surgeons, gastroenterologists, radiologists, oncologists, pathologists and nurses. Patients must have undergone standard evaluation: multidetector CT +/- other modalities, e.g. EUS. The patients should be reviewed at the MDT meeting as per standard protocol for that centre. Eligible patients for this study will include all patients with suspected pancreatic malignancy as defined in the inclusion criteria.

The decision on patient eligibility by the pancreatic MDT should take into account all clinical details and investigations undertaken for the patient under discussion. Multidetector CT with pancreas-specific protocols will be used as the standard for diagnosis in all centres. The number of lesions, size of lesions, morphological features (solid, cystic), any dilation of the bile duct and or pancreatic duct, vascular involvement and any extra-pancreatic disease will be recorded on the D1 CRF after patient registration.

If the patient is deemed eligible they will be reviewed in the outpatient clinic or as an inpatient and provided with a patient information sheet (Appendix A). Informed consent will be obtained after the patient has had sufficient time (at least 24 hours) to make a decision and prior to any baseline assessment and study registration. The diagnosis, stage and management plan from the MDT meeting will be recorded in the CRF as D1 at that point.

A log of all potential patients will be kept, including individuals who decide not to participate in or who are found to be unsuitable for the study. The LCTU will provide a 'Screening and Registration' log to each centre at the point of initiation

8.2. Study Registration

For patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria, the responsible clinician or delegate will contact the LCTU to register the patient. To ensure essential entry criteria are fulfilled, registration can only occur following the completion and forwarding of the study **REGISTRATION FORM** and **SIGNED INFORMED CONSENT FORM** by the investigators:

The registration documents should be faxed to the LCTU on Monday – Friday from 09:00 to 17:00, fax number: 0151 794 8247. Prior to faxing documents, site staff should telephone the study co-ordinator to inform them of the incoming registration fax.

Personnel from the LCTU will review the registration from, confirm eligibility and record essential demographic data. The Registration Form will be annotated with details of the unique study number allocated to the patient. The unique study number and date of entry into the study must then be recorded on the original Patient Screening & Registration Log and in the patient case notes. The original copy of the consent form will be retained in the patient's medical notes and must be available for inspection.

9. Assessments and Procedures

9.1. Schedule of assessments

Procedures		Screening (MDT)* ♦	Baseline (Day 0)*	D1	Additional Pet /CT	D2	D3 – Actual Management	Follow-Up Schedule: 12 weeks	24 weeks	36 weeks	48 weeks/ Study Completion	Premature Discontinuation	D4 – Reference Standard
Window for time points (All visit time points are from the Day 0 Baseline visit)					2 weeks ± 4 days			± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks		
Signed Consent Form			X										
Assessment of Eligibility Criteria		X	X										
Review of Medical History & Demography			X										
MDCT (± MRI/EUS/USS/ERCP)		X*♦	X♦										
Review of Concomitant Medications			X					X	X	X	X	X	
Urine pregnancy test (WCBA) ■			X										
Random blood glucose			X										
PET/CT Scan					X								
CA.19.9		X♦	X♦					X♦	X♦	X♦	X♦		
EQ-5D Quality of Life			X					X	X	X	X		
CSRI form			X					X	X	X	X		
WHO Performance Status			X					X	X	X	X		
Physical Exam	Complete		X										
	Symptom-Directed		X					X	X	X	X		
Assessment of Adverse Events					X								
Clinical Laboratory^	Chemistry U &Es LFT CRP Amylase	X♦	X♦					X♦	X♦	X♦	X♦		
	Haematology FBC Clotting Profile	X♦	X♦					X♦	X♦	X♦	X♦		
Record Diagnosis, management plan and staging				X		X	X						
Reference standard													X

* The patient may have results from one or all of the marked procedures

♦ Procedures carried out according to local practice with regard to patients with suspected pancreatic malignancy, these are not study-specific procedures.

■ Only to be conducted in women of child bearing age (WCBA)

9.2. Screening for study eligibility

Patients will be assessed for their eligibility for entry into the study during the local MDT meeting. Screened patients should have a suspected pancreatic malignancy with one or more of the following exploratory test completed to be considered for the study:

- Multidetector CT scan
- Serum bilirubin test
- Serum CA 19.9 test

The patient management plan and clinical decisions made at this point will be documented on the D1 CRF.

9.3. Baseline assessments

After patients have consented to study participation and signed the informed consent form, baseline assessments should be performed prior to study registration in order to confirm eligibility. The PET/CT scan should be performed within 2 weeks (± 4 days) of the baseline visit. This is to ensure patients are not delayed in their diagnostic and management pathway due to participation in the study. The baseline assessments include the following:

- Informed Consent – taken prior to any other study procedures
- Assessment of eligibility criteria
- Review of medical history & demography
- Review of concomitant medications
- EQ-5D Quality of Life
- WHO performance status
- Physical exam (complete and symptom-directed)
- CSRI questionnaire
- Urine pregnancy test (WCBA)
- Random blood glucose

The patients will undergo the following investigations according to standard clinical practice:
Clinical Laboratory

Chemistry

- U & Es (i.e. urea and electrolytes)
- LFT
- CRP
- Amylase
- CA.19.9

Haematology

- FBC
- Clotting Profile

Further diagnostic investigations including:

- Multidetector Computed Tomography (MDCT)
- Endoscopic Ultrasound (EUS)
- Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Magnetic Resonance Cholangiopancreatography (MRCP)

9.4. PET/CT

The patients will then undergo FDG PET/CT scanning within two weeks following consent and baseline visit(s). Should the PET/CT scan not be conducted within two weeks the LCTU should be informed. If the

research site deems the resulting delay in patient management to be unacceptable the patient should be withdrawn from the study and the LCTU informed of this decision.
The PET/CT scan result will first be documented independently of other clinical information. The patient will then be discussed again by the investigator or at the MDT with the results of the PET/CT available. The management decision will be documented at this point D2 (see section 10.2).

9.5. Planned assessments during follow-up phase

Planned study visits will take place every 3 months or when clinically indicated post baseline for 12 months. Each patient will undergo planned management according to standard practice; which may involve pancreatic resection, biopsy, clinical +/-radiological +/-CA19.9 follow up, best supportive care or other therapy such as chemotherapy. All procedures, treatment and outcomes will be recorded on each follow-up CRF form. Follow up assessments have been scheduled for every 3 months to mirror local standard practice throughout the patient journey as closely as possible. Due to the regional distribution of pancreatic referral centres and geographical difficulties the schedule of follow up visits may not be able to be adhered to in every case. If in person visits to research sites are not possible for patients, information collection at follow up time points should be completed over the phone to ensure quality of life and health economics data is collected. All patients must attend their final 12 month follow up visit if still on study at the participating research site.

9.6. EQ-5D and CSRI Questionnaire

The patient will be asked to complete a short validated quality of life questionnaire (EQ-5D) (Appendix D) and a health Economic Form (CSRI – Appendix E) at each study visit. These completed forms should be submitted to the LCTU with the corresponding CRF form. Should patients be unable to attend follow up visits in person the EQ-5D and CSRI questionnaires should be completed over the telephone. A standard script for telephone administration of the EQ-5d questionnaire (Appendix I) will be followed by the researcher.

9.7. WHO Performance status

Performance status must be assessed at each follow-up visit according to the WHO Performance Status (Appendix F) and recorded on the CRF.

9.8. Laboratory Assessments

There are no mandatory laboratory assessments required as part of the study. Local standard practice should be followed throughout the patient journey. However any laboratory investigations conducted should be recorded in the follow-up CRF.

9.9. Concomitant Medication

Data on Concomitant Medication will be collected at the baseline and at each 3 monthly follow-up visit and will contribute to the Health Economics analysis. There are no restrictions on what medication can be used. All chemotherapy should be recorded as standard.

10. Decision Points

10.1. D1

The diagnosis, stage and management plan from the MDT meeting will be recorded in the CRF as D1 at this point. D1 is the decision made by the clinicians UNBLINDED using the usual diagnosis strategy based on the multidetector CT and MDT meeting outcome and following local practices. The decisions will be categorised according to diagnosis, staging and management.

10.1.1. Diagnosis

Diagnosis will be categorised by the following options:

1. Pancreatic ductal adenocarcinoma
2. Peri-ampullary cancer
3. Cholangiocarcinoma
4. Benign cystic neoplasm
5. Malignant cystic neoplasm
6. Pancreatic pseudocyst
7. Chronic pancreatitis
8. Autoimmune pancreatitis
9. Acute pancreatitis
10. Neuroendocrine tumour
11. Lymphoma
12. Metastasis from non pancreatic primary neoplasm
13. Recurrent pancreatic cancer post resection
14. Normal pancreas
15. Other

10.1.2. Staging

Staging will be categorised according to the following options:

1. Resectable (UICC TNM 7th Edition, 2009, classification stage 0, IA, IB, IIA, IIB) [46]
2. Borderline resectable, i.e. defined as up to 2cm of portal/superior mesenteric vein involvement for 180^{o} circumference.
3. Unresectable (UICC TNM 7th Edition, 2009, stage III and IV)
4. Other

10.1.3. Management

Management will be categorised according to one or more of the following options:

1. Resection (+/-prior laparoscopy)
2. Biopsy (EUS/percutaneous)
3. Drainage procedure, e.g. stent or surgical bypass
4. Chemotherapy/trial
5. Best supportive care
6. Clinical follow up +/- further investigation
7. No further management required
8. Other

10.2. D2

After the additional PET/CT scan has been performed the diagnosis, stage and management plan will be re-evaluated by the investigator or at another MDT meeting and will be recorded in the CRF as D2 at that point. Categories will remain the same as D1.

10.3. Certainty

For all the diagnosis, staging and management options listed in D1 and D2 the MDT will record a level of certainty categorised as:

1. Very certain
2. Moderately certain
3. Uncertain

10.4. D3

The actual diagnosis and management of each patient will be recorded on the D3 CRF, as this may differ from the D2 time point. Include any pathology details + report (resection/biopsy), operative details and actual therapy administered.

10.5. D4

10.5.1. Reference Standards

The reference standard for diagnosis will be a clinical judgement made by an independent panel based on histology (either biopsy or resection) or clinical outcome at the 12 month assessment. Estimated patient numbers for biopsy are 150, resection 300 and follow up 150. The panel will agree on the appropriate staging for each patient with pancreatic cancer and appropriate management – to be used as reference diagnoses D4.

10.5.2. Stage 1

The panel will initially receive a patient histology report for the target conditions:

- Pancreatic cancer (for the primary objective)
- Stage of pancreatic cancer (UICC TNM 7th Edition, 2009, classification as above for resectable, borderline resectable and unresectable disease)
- Chronic pancreatitis
- Particular types of pancreatic tumour.

In addition to this they will be provided with information about the clinical status of the patient at 12 months (but excluding all information from investigations made at baseline and the PET/CT test results). This will be according to the minimum dataset of the Royal College of pathologists [47], in a standard format for resection histology, this will include pathological staging (pTNM) for tumours.

10.5.3. Stage 2

If the panel is unable to make a firm reference diagnosis based on the above information, results of baseline investigations will be released but not the PET/CT investigation.
The two stage process is planned so that the panel's initial decision is not contaminated by the standard work up of either set of test results, and never by the PET/CT scans results and avoids incorporation bias. Finally the panel will also be asked to judge the appropriateness of management for each patient and if a change prompted by PET/CT was appropriate.

11. NCRI PET Core lab

11.1. Screening PET/CT Core Laboratory

A Core Pet/CT Laboratory Facility has been set up as part of the NCRI PET Research Network, Clinical Trials Network at the PET Imaging centre at St. Thomas's Hospital, London. Their role will cover the following:

- Co-ordination of imaging studies in liaison with clinical trials units
- Data transfer, QC and collation processes
- Ongoing QC, Audit and approval of PET Centres
- Specify patient confidentiality, data transfer and related issues.
- To provide advice and guidance to all study centres throughout the study.
- Advice on protocols for PET/CT acquisition and processing

11.2. Processes for PET/CT scanning

Given that PET/CT scanning is a relatively new technology in the NHS, national standardised protocols and quality assurance procedures are actively under development. This national study aims to be widely applicable to many centres and will involve the use of both fixed and mobile scanners following a strict quality assurance programme.
Prior to a site being given the green light to begin recruitment accreditation must be granted by the Core Lab. This will be used to evaluate and resolve image transfer and other quality issues to ensure images acquired from participating centres are of comparable quality.
Individual study participant QC reports will be issued by the core lab on PET/CT images

11.3. Data Transfer

PET Centres submitting data should ensure the data is anonymised and in DICOM Part 10 format. The submitted images must include the attenuation corrected PET, non-attenuation corrected PET and the CT.
The recommended method for electronic data transfer from NHS PET Centres is via the NHS Secure File Transfer Service.
All other sites with appropriate internet access should use the NCRI Core Lab FTP server.

Full instructions can be obtained at the following link; http://www.ncri-pet.org.uk/index.php?option=com_content&view=category&layout=blog&id=14&Itemid=7

Data submitted on DICOM CD should be sent to the NCRI Trials Physicist:
Lucy PikePET Imaging CentreLG Floor,
Lambeth Wing
St Thomas' Hospital
LondonSE1 7EH
Tel: 020 7188 7188 ext 51636
Fax: 020 7620 0790
Email: lucy pike@kcl.ac.uk
lpike@nhs.net

11.4. Recommended standardised criteria for reading and reporting PET/CT

All PET/CT scans will be reported locally according to an agreed protocol (Appendix G). The standardised protocol and criteria for performing and reading of PET/CT scans will be provided to all participating PET/CT centres by the LCTU. PET/CT scans must be reported using manual visual analysis technique, sufficient for the results to be recorded on the PET/CT CRF. In addition it is requested that the Standard

Uptake Values (SUVs) of the scans should also be assessed and reported, to enable the results to be recorded in the PET/CT CRF.

11.5. PET/CT Central Reporting

A central PET/CT reporting facility has been established at the Paul Strickland Scanner Centre at Mount Vernon Hospital, in addition to the designated Core Lab, to provide central PET/CT reports independent of the local hospital, reviewed by two experts in clinical PET/CT and to perform second stage quality assurance on all PET/CT scans. Data will be transferred from the Core lab to the Central reporting facility. Central clinical reports will be produced independently by two designated radiologists expert in PET/CT. If there are any significant differences in the local and central reports the local and central laboratory radiologists will confer and agree on a final report and the principal investigator will be informed. To ensure a full report can be produced the central reporting facility must be in receipt of the following;

- PET/CT Report
- Clinical Details
- PET/CT Request
- CT scan from MDT meeting

Contacts at the central reporting facility;

Dr Wai Lup Wong (Clinical Queries)

Paul Strickland Scanner Centre,
Mount Vernon Hospital,
Northwood HA6 2RN.
Tel: 01923 844283
Fax: 01923 844600
MOBILE: 07903568508
Email: wailup.wong@nhs.net

Dr Bal Sanghera (QA Queries)

Paul Strickland Scanner Centre
Mount Vernon Hospital
Northwood. HA6 2RN.
Tel : +44 (0)1923 844 392
Fax: +44 (0)1923 844 600
MOBILE: 07904105884
Email: bal.sanghera@nhs.net

11.6. PET/CT Protocol

Please see Appendix G

12. Statistical Considerations

12.1. Outcome measures

Primary:

1. To determine the incremental diagnostic accuracy and impact of PET/CT in addition to standard diagnostic workup in patients with suspected pancreatic cancer.

Secondary:

1. To evaluate changes in diagnosis, staging, and associated intended patient management through the addition of PET/CT
2. To determine cost effectiveness of the addition of PET/CT in the diagnosis, staging and management of pancreatic cancer.
3. To evaluate the impact of the addition of PET/CT in differentiating pancreatic malignancy from chronic pancreatitis.
4. To identify which groups of patients would most benefit from PET/CT.
5. To report the incremental diagnostic value of PET/CT for particular types of pancreatic tumour.
6. Data will be analysed in separate cohort groups; the subgroups will be as follows (identified through baseline assessment and D1 data):
    a) No mass on CT
    b) Chronic pancreatitis
    c) Resected tumours with no recurrence on CT
    d) Raised tumour markers but no mass on CT
    e) Dilated pancreatic duct on CT but no mass on CT

12.2. Sample Size

A previous meta-analysis [35] reported a sensitivity of 81% and specificity of 66% for the diagnosis of pancreatic cancer with standard CT. The primary objective of this study is to investigate the incremental value of PET/CT. To be of clinical value to the diagnostic work-up the addition of PET/CT should increase the sensitivity from 81% to 90% and specificity from 66% to 80%. Using methodology [49] for a paired design, the number of diseased and non-diseased subjects required to have 80% power to detect these differences at the 5% (two sided) significance level range between 87 and 281 (diseased) and 57 and 221 (non-diseased) depending on the assumption made about the correlation between the test errors (false positives and false negatives). To ensure adequate power, the largest of these (281 diseased patients = 600 pancreatic cancer patients assuming 47% prevalence) will be the initial target for recruitment As the sample size for this paired design is highly dependent upon the correlation between the test errors between the tests (false positives and false negatives). The more closely related the errors, the higher the sample size required. An interim analysis will estimate this correlation and confirm the prevalence estimate after 200 patients have been recruited and reference standard obtained. The sample size will then be refined accordingly. This initial target of 600 patients is likely to be the absolute maximum sample size required.

12.3. Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at regular intervals (at least every six months) for review by an Independent Safety and Data Monitoring Committee (ISDMC). These analyses will be performed at Lancaster University. The ISDMC will be asked to give advice on whether the accumulated data from the study, together with results from other relevant studies and trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the study and the general clinical community. If a decision is made to continue, the ISDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The ISDMC will make recommendations to the Trial Steering Committee as to the continuation of the study.

A confidential report of the interim analysis has been approved by the ISDMC. The recommendations have been approved by the TSC and the final sample size set at 500 patients.

12.4. Statistical Analysis Plan

The analysis will focus on investigating incremental diagnostic accuracy and incremental diagnostic impact. Diagnostic accuracy will be investigated by comparing the baseline diagnosis (D1), and the results of the PET/CT scan with the reference diagnosis (D4); diagnostic impact by comparing the baseline (D1) and post PET/CT (D2) diagnoses with the reference diagnosis (D4).

The diagnostic impact of standard work-up will be estimated by comparing diagnostic decisions made at D1 with the reference diagnosis made at D4 for each of the target conditions (pancreatic malignancy, chronic pancreatitis and the tumour types) and expressed as sensitivities and specificities together with 95% confidence intervals (computed using binomial exact methods). To evaluate the accuracy of staging by standard work-up the analysis will be restricted to individuals with pancreatic malignancy diagnosed at the reference diagnosis. The accuracy of the revised diagnoses made after PET/CT will be assessed in the same way making comparisons between diagnostic and staging decisions made at D2 with the final reference diagnosis.

The initial analysis of the incremental benefit of PET/CT over standard work-up will be assessed through comparing the sensitivity and specificity of diagnostic decisions D1 and D2, in both absolute and relative terms. Tabulations will be created of cross-classifications of the D1 and D2 diagnoses for diseased and non-diseased to investigate the within patient changes induced by the PET/CT scan and their significance assessed using McNemar's test for paired data. This change will be computed for each of pancreatic malignancy, chronic pancreatitis, and the tumour types. Subgroup analyses using GEE regression modelling (taking account of paired data) will be undertaken to investigate whether test performance varies according to presenting conditions.

The incremental accuracy of PET/CT over standard workup will be investigated using regression modelling following the Knottnerus approach summarised by Chan et al. This allows the modelling of a sequence of tests through creative construction of indicator variables, which takes into account the non-independence of test results, but does not alter the value of previous test results when subsequent tests are added to the model. It also allows expression of the incremental diagnostic value as likelihood ratios.

Comparison of the diagnostic accuracy and diagnostic impact of PET/CT will allow investigation of whether the clinicians in the study were rationally incorporating results of the PET/CT scan into their diagnoses.

Further paired analysis will be undertaken in a similar manner to investigate whether PET/CT introduced changes to patient management plans, and levels of confidence associated with diagnostic decisions.

13. Health Economic Analysis

13.1. Research Objectives

The research objectives of the health economics component are:

1. To provide cost-effectiveness analysis of PET/CT in addition to standard diagnostic workup in the diagnosis, staging and management of pancreatic cancer.
2. To develop the economic model for the simulation of costs and outcomes over 5 years of using PET/CT in addition to standard diagnostic practice in patients with suspected pancreatic cancer.

13.2. Research Methodologies

1. *Systematic review of application of Markov model in medical decision making*. We will undertake a review of economic literature in this field to identify how economic modelling has been used to explore the cost-effectiveness of diagnostic techniques and patient management.

2. *Measurements of Costs.* From an NHS perspective [51-53], we will fully cost the addition of PET/CT scanning to standard diagnostic and disease management procedures, and record participant's primary and secondary care service use , which will be costed using National Reference Unit Costs [54,55]. Costs will be collected using the validated Client Service Receipt Inventory (CSRI) questionnaire after consent and at each three-month outpatient review. Specifically, we are interested in seeing how the patient pathway and associated use of health services changes as a result of adding PET/CT scanning to the diagnosis of suspected pancreatic cancer.

3. Cost-effectiveness Analysis. Effectiveness will be evaluated in terms of incremental diagnostic value of PET/CT in addition to standard diagnostic workup with CT. Incremental cost-effectiveness ratio will indicate the change in cost and effectiveness of adding PET/CT to standard CT procedure. The uncertainty of cost-effectiveness analysis will be addressed using bootstrapping in order to provide an estimate of the probability distribution and the confidence interval. This analysis will produce the cost-effectiveness acceptability curves (CEACS) to quantify and graphically represent the uncertainty.

4. Measurement of Utility. The patient will complete a short quality of life questionnaire (EQ-5D) after consent and at each three-month outpatient review. EQ-5D is a standardised instrument for use as a measure of health outcome and provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care http://www.euroqol.org/.

5. *Construction of an Economic Model*

This in depth cohort study offers an opportunity to collect prospective patient level, clinical and economic data which can populate an economic model to use to illustrate the likely cost-effectiveness of adding PET/CT to the diagnosis of suspected pancreatic cancer. We will use a decision analytic model to assess the cost-effectiveness of PET/CT in addition to current practice in management of suspected pancreatic cancer as compared with current practice alone. This approach will:

1. Aim to incorporate all appropriate clinical evidence gained from this study and from the literature into this model.
2. Use this model to compare the cost-effectiveness of PET/CT scanning in the diagnosis and management of pancreatic cancer with usual diagnostic practice, (reflecting the full range of existing technologies) and reflect uncertainty in evidence in the conclusions from the analysis undertaken [53, 56-58].
3. A decision analytic model will be constructed to show the lifetime costs and outcomes of adding PET/CT scanning technology to usual diagnostic practice for this patient group. This model will be used to predict costs and benefits associated with changes in diagnosis, subsequent management of patients and expected benefits in survival and health related quality of life. It will allow the generation of cost effectiveness planes and acceptability curves to enable communication of the probability that PET/CT scanning is a cost effective addition [59].

14. Quality Assurance

14.1. Central QA for CT scans

There will be central radiology review for quality assurance. Central radiology review of 10% of multidetector CT scans will be carried out by Dr Jonathan Evans, Consultant Radiologist (Royal Liverpool University Hospital NHS Trust). Where there are significant differences between the reports of the local radiologist and the central radiology reviewer that may affect patient management, the central radiology reviewer and the participating centre radiologist will confer and a final report will be agreed.

CT scans, randomly selected from each centre for central reporting, will be requested by the LCTU following registration of the patient. A proforma will be sent from the LCTU to the recruiting hospital (email or fax) to request the anonymised CT images on disc. These will be sent directly to:

Dr Jonathan Evans
Consultant Radiologist
Department of Radiology
Royal Liverpool and Broadgreen University Hospital NHS Trust
Prescot Street
Liverpool
L7 8XP

Email: Jonathan.Evans@rlbuht.nhs.uk
Tel no: 0151 706 2758
Fax no: 0151 706 5799

Once a disc has been received it is loaded into an RA600 import workstation. The scan is then opened on the RA600. The images will be exported from the RA600 to PACS. Once all the images have arrived on PACS, these are then post-processed and the radiologist is then able to report the images.

All reports which are matching will be sent to the LCTU. Where there is a difference between the original report and the central report, this report will be sent to the Principle Investigator at that site and the central radiology reviewer and the participating centre radiologist will confer and a final report will be agreed.

14.2. Pathology

The central pathology review will be carried out by Dr Fiona Campbell, consultant Gastrointestinal Pathologist (Royal Liverpool and Broadgreen University Hospital Trust)

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

Histology slides requested by the LCTU for central review will be sent to;
Dr Fiona Campbell
Consulatant Gastrointestinal Pathologist
Department of Pathology
Royal Liverpool University Hospital
5th Floor Duncan Building
Daulby Street
Liverpool
L69 3GA

14.3. Biopsies

The histology slides from all the biopsies will be reviewed centrally these will be requested after completion of actual diagnosis and management (D3).

14.4. Resection Specimens

Approximately 10% of all resection specimens will have the histology slides reviewed centrally by Dr. Fiona Campbell. These will be selected at random. However at least 2 specimens will be selected from each centre. As with the biopsies these will be requested by the LCTUafter completion of actual diagnosis and management (D3).

15. Pharmacovigilance

15.1. Definitions

Adverse Event (AE)
Any new untoward medical occurrence in a research participant to whom a medicinal product/clinical investigation has been administered, including occurrences which are not necessarily caused by or related to that product/investigation.

Serious Adverse Event (SAE)
Any adverse event 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) 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.

*'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.

15.2. Reporting Procedures

Adverse events that occur **within 24 hours** of completing the PET/CT scan will be recorded in the Adverse Event case report form.

Completed AE forms will be requested from all research sites as part of the 3 month follow-up Case Report Forms (CRF) collection or upon death

All serious adverse events occurring in patients **within 24 hours** of completing the PET/CT scan should be reported to the LCTU within 24 hours of the research site becoming aware of the event. The LCTU will acknowledge receipt of the SAE to the reporting site. Any questions concerning adverse event reporting should be directed to the LCTU in the first instance.
All events occurring after 24 hours post scan DO NOT need to be reported to the LCTU.

15.3. Notes on Serious Adverse Event Exclusions

Do not include:

- Elective hospitalisations for the treatment of the primary disease and its effects
- Elective hospitalisation for social reasons
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by the clinical investigation

15.4. 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 the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
Life threatening
Death

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

15.5. Relationship to PET/CT

The assignment of the causality should be made by the investigator responsible for the care of the participant. Relationship to PET/CT will be recorded as Yes/No on the SAE form.

All SAEs will be unexpected and therefore reported to the ARSAC certificate holder and radiopharmacy. These will be reported to the sponsor within agreed timelines.

15.6. 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.

16. Ethical Considerations

The study will be conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments (Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996). The study will be conducted in compliance with the Medicines (Administration of Radioactive Substances) Regulations 1978 ('MARS') and the principles of Good Clinical Practice.

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

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

This study will assess the effects of adding PET/CT to the usual standard of care for patients with suspected pancreatic cancer. The risks will be of the PET/CT itself and any possible delay to the patients diagnostic and management pathway. The risks of PET/CT scan are of the radiotracer ^{18}F –FDG itself, allergic reaction to the radiotracer and radiation exposure from the CT scan. Allergic reactions to radiopharmaceuticals may occur but are extremely rare and are usually mild. The doses of radiotracer administered are small typically 8mSv for adults using 400MBq. The radiation dose from the CT scan can be low (e.g. an effective dose of about 7mSv) The risk of increased carcinogenesis associated with radiation exposure is outweighed by the benefits of correctly identifying patients who will can undergo surgery and also preventing unnecessary surgery in others. The scans will be performed in a timely manner to minimize any delay**.**

16.1. Ethical Approval

Ethical approval will be applied for from the Integrated Research Application System (IRAS). This will include approval from the National Research Ethics Service Committee, NHS R&D and Administration of Radioactive Substances Advisory Committee (ARSAC)

All participating sites must undergo site specific assessment (SSA) via the IRAS conducted by their local R&D department. A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to the LCTU before patients are entered. The LCTU should receive notification of positive SSA for each new centre prior to allowing any patient registration.

After a patient has been registered into the study, the clinician is free to withdraw the patient at any stage if he/she feels it is in the best interest of the patient. However the reason for doing so should be recorded and the patient will remain within the study for the purpose of follow-up and data analysis. Similarly, the patient remains free to withdraw at any time from the protocol and study follow-up without giving resins and without prejudicing further care.

16.2. Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a research study and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTU coordinated studies. 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 study 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 Sheet and Informed Consent form, describing in detail the study interventions/products, study 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 study may be obtained will be provided.

After being given adequate time to consider the information (at least 24 hours), 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 study 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.

17. Regulatory Approval

A Clinical Trials Authorisation is not required because this is a post-market clinical study on a CE marked device being used for its intended purpose which involves protocol driven follow up visits additional to standard care. Therefore according to annex B of the approval of medical device research guidance from the National Research Ethics Service this only requires ethical approval and NHS permission.

18. Data Capture Methods

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

Each Investigator and/or designated personnel will be issued with a password and instructions for the web-based CRF system after the 'Green Light' for that site has been given. Investigators will be instructed to download and print off forms as and when they are required and not to save them to their local computer. This ensures the investigators will always have to go to the website each time they need a new form and so if there have been any updates to the CRFs the site staff will therefore always be using the latest versions. The Investigator must ensure a separate CRF is printed off for each patient enrolled and that a photocopy is taken for their records prior to submitting data to the LCTU. The CRFs have been written following the LCTU Standard Operating Procedures.
The CRFs must be kept on file by the investigator and maintained in an up-to-date condition at all times. The investigator, or a designated sub-investigator, must sign and date the bottom of the CRFs, as indicated.

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

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

19. Study Monitoring

Central and site monitoring is conducted to ensure protection of patients participating in the study, and that study procedures, laboratory and data collection processes are of high quality and meet sponsor requirements. A risk assessment for the study will be carried out, prior to the start of patient registration, to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

19.1. Risk Assessment

In accordance with LCTU Standard Operating Procedures and the requirements of the sponsor organisation a study risk assessment will be completed in partnership with:

- Representatives of the study co-sponsors (The University of Liverpool and the Royal Liverpool and Broadgreen university Hospital Trust)
- Chief Investigator
- Study Co-ordinator
- Study Statistician
- LCTU Operational Director
- CTRC Senior Management Team

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

The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:
Score ≤33% = Low risk
Score >33 to ≤ 67% = Moderate risk
Score >67 to ≤ 100% = High risk
The risk assessment (document number RAPET001.1 in the LCTU Document Management System) resulted in an overall percentage of 19.5% and thus the study is considered low risk.

19.2. Source Data

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

19.3. 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 study. (ICH E6, 1.52)

Data recorded in the CRF should be consistent and verifiable with source data in source documents other than the CRFs (e.g. medical records, laboratory reports and nurse's notes). Each participating site should maintain appropriate medical and research records for this study.

For data where no prior record exists and which are recorded directly in the CRF (e.g. inclusion/exclusion, adverse events and Quality of Life questionnaire), 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 the patient information, study screening, study number, study treatment and the fact that the patient is participating in a study should be added to the patient's medical record contemporaneously

19.4. Monitoring at the LCTU

19.4.1. The Green Light Process

The Green Light Process in place at the LCTU means that no patients can be registered at a particular site without the green light having been given. It ensures that all approvals must be in place, all contracts/agreements signed and all study-specific and ICH GCP training received by site research staff before patients can enter the study. Once a site has been given the green light (which can only be granted by the study coordinator (SC), they will be issued with screening numbers which are necessary for registration to take place and a password for the online CRF download.

19.4.2. Site Research Staff

All site research staff involved in the study must be included on the delegation log. The PI at each site signs off on the delegation log only those staff members he/she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the data management plan) against staff named on CRFs, SAE reports and registration forms.

The SC ensures that all delegated staff have documented study-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the SC and on a continuous basis throughout the study when new staff are added to the delegation log. Sites are supplied with copies of training aids presented at site initiation to provide a constant reminder of key study issues. Delegated site research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (to be renewed every 2 years as suggested by ICH GCP), an automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Automated 6-monthly email reminders (from site opening) are sent to sites requesting that an updated delegation log is faxed to LCTU. On receipt of updated delegation logs, the SC ensures that new staff have submitted their CVs and date of last ICH GCP training, as well as providing them with study-specific training.

19.4.3. Registration

The SC verifies that all site research staff have attended study-specific training relating to eligibility screening and the informed consent/registration process. Prior to randomisation, the SC/data manager (DM) carry out a check of all consent forms sent to the LCTU. This includes checking that the patient is eligible, the correct versions of the Patient Information Sheet (PIS) and Informed Consent Form (ICF) have been used, and the patient and clinician signatures are present and dated on the same day. LCTU staff receive appropriate registration training and there is always office cover to ensure the registration procedure is carried out correctly.

19.4.4. Patient Confidentiality

All LCTU and site research staff have received ICH GCP training and are thus aware of the importance of patient confidentiality. The SC/DM consistently check that the CRFs sent to LCTU are all anonymised and are identifiable only by study number (except for signed consent forms, which are stored in a locked

cabinet in the LCTU, separately to the CRFs). The SC will monitor site performance on maintaining patient confidentiality and will provide additional training if a particular site sends any patient identifiers to LCTU (other than on the signed consent form).

19.4.5. Recruitment

The SC will produce monthly recruitment reports, to allow the ISDMC, TSC and TMG to regularly review recruitment across sites. Slow or inconsistent recruitment will trigger further action centrally. The SC may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. SC will check that the study is being actively promoted at sites, and site recruitment schedules will be reviewed during the course of the study as necessary.

19.4.6. Protocol Violations/Deviations

All protocol violations and deviations are recorded by the SC in the study site status database, and are included in the regular ISDMC reports. The SC sends details of all protocol violations and deviations to the CI as soon as the LCTU is made aware of such occurrences, and any that are considered to be a potential serious breach would be forwarded immediately to the Co-sponsors. Details of all other protocol violations and deviations are sent to the Co-sponsors on a monthly basis for their review. If it is noted that a particular site is making consistent protocol violations or deviations, additional training will be provided by the SC.

19.4.7. Withdrawals, loses to follow-up and missing data

The SC will produce reports on withdrawals, losses to follow-up and the quantity of missing CRFs/data across sites for review by the LCTU business meeting, TMG, TSC and ISDMC. Identified problems will be discussed and remedial action taken as necessary.
As outlined in the data management plan, the SC/DM will check that the End of Study CRF is completed for all withdrawn patients (including the reasons for withdrawal). The SC will compare withdrawal rates and reasons for withdrawal across centres, paying particular attention to withdrawals close to date of randomisation. If a certain site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

19.4.8. Data Management Plan

CRF data entered into the MACRO database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the study protocol. The MACRO database used for this study includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised within the MACRO database and emailed to site. A complete log of discrepancies and data amendments is automatically generated by MACRO, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue. Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in submitting CRFs.

19.4.9. Statistical Monitoring

Central statistical monitoring will be carried out by the study statistician prior to the production of each ISDMC report. Eligibility criteria and informed consent are checked to ensure all are documented and satisfied. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight

inconsistencies), as well as providing a record of the degree of missing CRFs and follow up visits, and missing baseline and outcome data. Safety and withdrawal data are also reviewed for completeness.

If there is compelling evidence to suggest that data from a particular site may be fraudulent, the SC may request a site visit to carry out source document verification of patient case notes and other source documentation.

19.4.10. The LCTU Staff

All LCTU staff will receive regular ICH GCP training, have in-house training records and undergo regular Individual Performance Review (IPR) sessions, all of which are used to ensure that appropriate training is received and any problems identified and resolved in a timely fashion.

19.5. Clinical Site Monitoring

19.5.1. Direct Access to Data

Site monitoring may be deemed to be necessary as a result of central data checks. 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. Each PI therefore permits study related monitoring, audits, ethics committee review and regulatory inspections by providing direct access to source data/documents. As this also affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

19.5.2. 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. Biopsy samples and paraffin blocks will be transferred to the 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.

19.5.3. Record Retention

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File, until 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 study data can be compared against source data after completion of the study. 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.

Essential documents should be retained until at least 2 years after the last patient has competed the study. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the LCTU by recruiting centres. This requires that name data will be transferred to the LCTU, which is explained in the PIS. The LCTU will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

20. Financial Arrangements

There will be a per patient payment of £230 to support patient recruitment and consent, consultant and research nurse time for CRF completion when patients are seen in outpatients, Quality of Life form completion, ordering and arranging PET/CT scans within 2 weeks and ensuring treatment and follow-up is correct and data is recorded accurately.

21. Study Oversight Committees

21.1. 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 LCTU Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the study and will meet approximately 3 times a year.

21.2. Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, Mr Ross Carter; independent experts in the field of PET/CT, Mr Terry Jones and Dr David Smith; biostatisticians, Gillian Lancaster and Jon Deeks and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the study and provide advice through its independent Chairman. The ultimate decision for the continuation of the study lies with the TSC.

21.3. Independent Safety and Data Monitoring Committee (ISDMC)

The independent Safety and Data Monitoring Committee (ISDMC) consists of an independent chairperson, Dr Ian Chau, expert in clinical oncology, plus 2 independent members: Sue Chua who is an expert in the field of PET/CT and Lucy Kilburn an expert in medical statistics.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, study conduct and external data. The ISDMC will first convene after 50 patients recruited and will then define frequency of subsequent meetings (at least every six months).

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

22. 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 (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the study's Chief Investigator(s), Statistician(s) and Study Manager(s) involved at least. The members of the TSC and ISDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication

23. Protocol Amendments

23.1. Version 1 (12/01/2010)

Original version submitted to Ethics Committee for review

23.2. Version 2 (01/03/2011)

23.2.1. Admin Changes

Replacement of word “Trial” with “Study” throughout the text of the protocol.
Replacement of “PET-CT” with “PET/CT” throughout the text of Protocol
Expansion of “MDCT” to multidetector CT throughout the text of the protocol to avoid confusion with MDT – Multidisciplinary team meeting.
Change of contact details to reflect LCTU moving premises
Change of details of approval signatory for the University of Liverpool
Protocol summary page; clarification of update of inclusion and exclusion criteria and update of number of sites
Schematic of study design altered to take into account the change that Diagnosis 2 (D2) assessment to be made by either Principal investigator decision or at a second MDT
Change of fax details for registration of patients
Additional acronyms added to the glossary and formatting changes made
Addition of contact details of central pathologist
Clarification of members of Trial Steering Committee (TSC) and Independent Safety Data monitoring Committee (ISDMC)
Appendix A Patient Information Sheet insertion of proposed version 5
Appendix E Client Service Receipt Inventory (CSRI) Questionnaire insertion of propose version 3
Appendix H Update of list of potential research sites and principal Investigators
Appendix I Addition of UICC 7th Edition (pancreas section extract) TNM staging classification for reference

23.2.2. Inclusion Criteria

Alteration of Inclusion criteria 4; "Able to attend for up to 12 months follow up."

23.2.3. Exclusion Criteria

Addition of a third exclusion criteria; “Patients with poorly controlled diabetes”

23.2.4. Schedule of assessments

Inclusion of random blood glucose test at base line to determine if patients are eligible for the research project under the new exclusion criteria

23.2.5. Staging

Clarification that 7th edition, 2009 of UICC TNM staging classification will be used for the histopathological assessments.

23.2.6. Decision Points; Diagnosis 2 (D2)

Assessment for Diagnosis 2 (D2); Diagnosis can be made following discussion at 2nd MDT or by assessment made by principal Investigator.

23.2.7. NCRI PET Core Lab

NCRI PET Research Networks, Clinical Trials Network facility at St. Thomas’s Hospital London replaced Paul Strickland Scanner centre. This facility has been created to provide core lab functions in a standardised format for all clinical trials involving PET scanning. Core lab function, details and data transfer procedures updated.

Paul Strickland Scanner centre has retained central reporting function (clinical) responsibilities and second stage quality assurance function

23.2.8. Statistical considerations

To be able to determine secondary outcomes 3, 4 and 5 subgroups identified for the different types of patients going into the study.
Formal Interim analyses to be performed every 6 months rather than annually to reflect the period for recruitment.

23.2.9. Pharmacovigilance

Clarification that only Serious Adverse Events (SAE) as defined in the protocol should be reported to the LCTU within 24 hours of the research site becoming aware of them and that Adverse Events (AE) should be recorded on the Adverse Event case report form.

23.2.10. PET/CT Protocol

Clarification of minimum reporting requirements for local and central PET/CT reports

23.3. Version 3 (01/09/2011)

23.3.1. Independent Safety and Data Monitoring Committee (ISDMC)

Frequency of meetings defined as every six monthly

23.3.2. Participating Sites

Update to section 3: Protocol Summary. Number of sites
Appendix H list of participating sites removed.

23.3.3. Appendix A: Patient Information Sheet

Current version inserted into Appendix A

23.3.4. Appendix G: PET/CT Protocol

Suitable Fasting blood glucose level of patients able to undergo PET/CT scan increased from 7mmol/l to 10mmol/l.
Specific instructions included for research sites for preparation of patients with Type I and Type II diabetes mellitus.
Injected activity during PET/CT scan re-defined following update to information supplied in IRAS made during this amendment. Redefinition required to take account of variation in scanning equipment in participating centres
Redefinition of Positioning of patient for scanning: “Begin scanning at the groin and end at the base of the orbits”

23.4. Version 4 (09/09/2012)

23.4.1. Sample Size

Sample size redefined as 500 patients following interim analysis

23.4.2. PET/CT

Clarification of time lines for conducting PET/CT scan .

23.4.3. Planned assessments during follow-up phase

Clarification of assessment time points. Option for follow up to be conducted via telephone if patient unable to attend. Patient to attend research h site for final follow up visit

23.4.4. Concomitant medication

Clarification that concomitant medication data will contribute to Health Economics

23.4.5. PET/CT reporting

Central clinical reporting of PET/CT to be conducted by two independent experts in clinical PET/CT.

23.4.6. Appendix I: EQ-5D Health Questionnaire (English version for the UK) Script for telephone administration.

Addition of standard telephone script for EQ-5D questionnaire.

23.4.7. Administration

Miscellaneous admin changes

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Appendices

Appendix A: Patient Information Sheet

(To be presented on local headed paper)

PATIENT INFORMATION SHEET (Version 6: 30/06/2011)

The impact of combined positron emission tomography with computerised tomography scanning (PET/CT) in the diagnosis and management of pancreatic cancer.

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

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

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

Part 1

What is the purpose of the study?

This study aims to see if a combined positron emission tomography (a specific nuclear medicine body scan) and computerised tomography (PET/CT) will improve diagnosis in patients who may have a pancreatic tumour. At the moment patients who might have a pancreatic tumour have a number of scans and other tests to try and diagnose the tumour. It is important to be as accurate as possible because this will affect what treatment patients will receive and potentially the outcomes of that treatment. PET/CT scanning is already widely used across the NHS for the accurate diagnosis of a large number of cancers, but their role in patients with suspected pancreatic tumours still needs to be proven.

We hope that by including this particular body scan we will be able to find out whether it will be of benefit to patients and see if we need to use it in the future in all patients or not.

Why have I been chosen?

You have already had some tests which mean that you have an abnormality in the pancreas.

Do I have to take part?

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

What will happen to me during the study?

You will have a PET/CT scan. This will involve coming to hospital as an outpatient or inpatient to the nuclear medicine/radiology department or mobile scanner unit. The scanner is a large machine with a

round doughnut hole in the middle where you are scanned. You will lie on a scanning table that will move slowly through the hole. You will not have anything to eat for several hours before the scan although you can drink plain water (non sugary water). Your appointment card should give you details of about what to do for your scan. If you are diabetic you will receive special instructions before your scan. You will then have an intravenous injection of a very small amount of a radioactive substance (radiotracer) for the scan. The radiotracer is called 18-fluorine fluoro-deoxy-glucose (FDG), a radioactive form of glucose. The amount of radiation is very small and only stays in the body for a few hours. In addition to the injection the CT part of the scan exposes you to a small amount of radiation in the form of X-rays.
The FDG injected into your body is taken up by tissue where glucose is used for energy. It shows up cancers because cancers in general use more glucose compared to normal tissue. Following the injection you will rest for 90 minutes and then have the scan which will take about 30 - 50 minutes.

You will be seen in the outpatient clinic or on the ward as usual for your doctor. The results of your scan should be available in 1-2 weeks. Your doctor will discuss your diagnosis and treatment with you and tell you the results of your scan.

You will then undergo treatment as prescribed by your doctor. As part of the study you will be seen in the outpatient clinic for up to 12 months after starting on the study. This will be to see how you are getting on.

What are the alternatives for the scan?

If you decide not to participate in the study, then your doctor will discuss other options with you based on the existing diagnostic tests which have been undertaken.

Are there any side-effects associated with the scan?

No adverse effects have been associated with FDG to date and no side effects are anticipated as a result of the scan. Should you suffer any side effect as a result of the scanning procedure the nuclear medicine / radiology department would be able to treat you in this event. The injection site may be red at the time of injection but this will go away by the time the scan is done.

What are the possible benefits of taking part?

The information provided by the scan is unique and cannot be obtained from other types of scan. It may provide the most useful information needed to make an accurate diagnosis and decide what the best treatment for you will be. The results of this important study will be used to benefit future patients.

What are the possible disadvantages and risks of taking part?

The extra scan may mean an extra outpatient appointment to take into account the results of the scan. The study will aim to have the scan done and the result available in two weeks. Following your FDG injection the amount of radioactivity remaining in your body naturally decreases by half every 110mins (this is called the half life) and combined with going to the loo and passing urine or stools you can expect the radioactivity to have passed from your body for all practical purposes after about 24 hours. During this time we recommend little or no contact with pregnant women and children in case they are more sensitive to radiation.

The extra dose of radiation you will receive by undergoing the PET/CT is associated with approximately 1 in 1000 risk of developing cancer. This is similar to the levels of radiation you are exposed to from the natural environment over a course of several years. The National Radiological Protection Board consider this low risk

What if there is a problem?

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

Will my taking part in this study be kept confidential?

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

Contact for Further Information

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

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

Please contact_____
Name and Title

On_____

This completes Part 1 of the Information Sheet. If the information in Part1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the test that is being studied or a new test may become available. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue. If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

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

You can withdraw from the study at any time but we would like you to still attend with your doctor as needed. If you do not wish to continue attending hospital, we would be grateful if you would allow us keep in touch with your General Practitioner to let us know your progress. If you withdraw, information collected may still be used if you allow.

What if there is a problem?

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

If you are harmed by taking part in this research project, Liverpool University (the co-sponsor) will pay compensation where the injury probably resulted from: A procedure being tested or administered as part of the trial protocol, Any test or procedure you received as part of the trial, Any payment would be without legal commitment. The Co-sponsor would not be bound by these guidelines to pay compensation where: The injury resulted from a drug or procedure outside of the trial protocol or the Protocol was not followed.
If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints mechanisms should be available to you (if appropriate). In the event of defective product then you may have grounds for a legal action for compensation against the manufacturer, but you may have to pay for your legal costs.

Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at by the investigators who are involved in organising this research project. They may also be looked at by representatives of regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and nothing that could reveal your identity will be disclosed outside the research site. We will take all reasonable steps to protect your privacy.

Involvement of the general practitioner/ family doctor (GP)

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

What will happen to any samples I give?

We are not collecting samples extra to those usually taken by your doctors.

Will any genetic tests be done?

No genetic tests will be done.

What will happen to the results of the research study?

It is intended that once the study is complete a report will be written and the results will be published to make them available to the public. You will be given the opportunity to receive a copy of the results once the study is complete. The results may also be used to inform the appropriate authorities who may make the scan widely available. You will not be named or identified in any publication.

Who is organising and funding this research?

This research project is funded by the National Institute for Health Research as part of the Health Technology Assessment Programme, they are supporting this study by providing core funding for staff to co-ordinate this study and for the scans to be carried out. It is being sponsored by the Royal Liverpool and Broadgreen University Hospital NHS Trust and the University of Liverpool. Your doctor will not receive any payment for including you in this study.

Who has reviewed the study?

The study has been reviewed for scientific content by members of the HTA peer review committee and a National Research Ethics Service Committee has reviewed the study for ethical considerations. The study

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

Appendix B: Informed Consent Form

(To be presented on local headed paper)

PATIENT CONSENT FORM (please read carefully) – Version 1 Date: 12/01/10

The impact of combined modality positron emission tomography with computerised tomography scanning (PET/CT) in the diagnosis and management of pancreatic cancer.

Name of Researcher: _____

Please initial

1. I confirm that I have read and understand the information sheet dated …… (version .....) describing the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of my medical notes and data collected during the study may be looked at by responsible individuals involved in this research or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I give permission for stored pathological specimens to be used for this trial ☐

5. I give permission for a copy of my consent form to be sent to the Liverpool Cancer Trials Unit (where it will be kept in a secure location), to allow confirmation that my consent was given. ☐

6. I agree to allow my General Practitioner and any other relevant medical practitioner to be informed of my involvement in the study. ☐

7. I agree to take part in the above study. ☐

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

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

Appendix C: GP Letter

GP Letter – Version 1 Date: 12/01/10
(To be presented on local headed paper)

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

PET-PANC

The impact of combined modality positron emission tomography with computerised tomography scanning (PET/CT) in the diagnosis and management of pancreatic cancer.

Date and version: dd/mon/yyyy,

Patient name:…….

Date of Birth:……

NHS Number:……...

Dear Dr _____,

Following fully informed written consent of their parent/legal guardian, your patient , _____ (date of birth dd/mon/yyyy), has been entered to the above trial which will determine the incremental diagnostic accuracy and impact of PET/CT in addition to standard diagnostic workup in patients with suspected pancreatic cancer.

Please find enclosed a copy of the patient information sheet for this trial.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____ at _____(Hospital)

Tel: _____

Yours sincerely,

<<Name>>
<Position>>

Appendix D: Quality of Life Questionnaire – EQ-5D

Health Questionnaire

English version for the UK

EQ - 5D

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

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

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

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

I am not anxious or depressed ☐

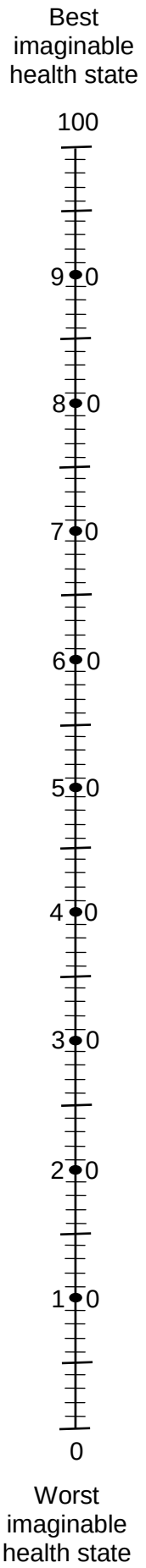
I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

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

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

Your own health state today



Appendix: E Client Service Receipt Inventory (Version 3. 01/03/11)

Client Service Receipt Inventory
(Service Use Questionnaire for Health Economics Analysis)

Sections 1.0 – 2.0 (Hospital Service Use and Community Based Service Use) should be completed by a project researcher in an interview with the PATIENT.

General Instructions to Interviewer

Before commencing with the interview, please ensure that the **Patient Registration Number** has been entered in the boxes below.

Subsequent processing of these questionnaires involves photocopying and the use of data scanning equipment. To ensure the smooth operation of the equipment, it would be appreciated if the following could be observed:

- Please complete the form using a **black** ballpoint pen.
- Please do not fold or crease the form.
- Please complete all the questions.
- Please enter your responses in the boxes/spaces provided, as instructed.
- Please use only a single line to delete mistakes and initial each such correction.

At the end of the interview please complete the remaining boxes to the right.

Thank you for your cooperation.

To be completed by the interviewer

Patient Registration Number: | | | |

Patient Initials: | | | |

Centre Name: _____

Which assessment is this? *Please tick the box*

Baseline	☐	9 month follow-up	☐
3 month follow-up	☐	12 month follow-up	☐
6 month follow up	☐		

Completed by (please print name): _____

Signed: _____

Interview date: | | | / | | | / | | | | |

d d m m y y y y

1.0 Hospital Service Use (Completed in the interview with the PATIENT)

Interviewer instructions: Please complete the table to show the hospital services that the PATIENT has used over the last 3 months.

Service	Name of ward, clinic, hospital or centre	Reason for using service (e.g. nature of illness, regular respite arrangement)	Unit of measurement	Total number of units received
Oncology **inpatient** ward			Inpatient day	
Medical **inpatient** ward			Inpatient day	
Continuing care/respite **inpatient** ward			Inpatient day	
Assessment/rehabilitation **inpatient** ward			Inpatient day	
Other **inpatient** ward			Inpatient day	
Intensive care **inpatient** ward			Inpatient day	
Inpatient consultations (including PAMs)			Appointment	
Outpatient visits (including consultations)			Appointment	
Accident and Emergency			Attendance	
Day hospital			Day attendance	
Other (1)			Please specify:	
Other (2)			Please specify:	
Other (3)			Please specify:	

This section asks about the health and social care services that you have used over the past 3 months.

2.0 Community Based Service Use (Completed in an interview with the PATIENT)

Interviewer instructions: Please complete the table to show the community based services that the PATIENT has used over the last 3 months.

Service	Number of home visits	Number of visits to surgery or clinic	Provider agency (please tick)				Average duration of contact (minutes)
			NHS	Local authority	Voluntary organisation	Private organisation	
Cancer nurse	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
General practitioner	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Practice nurse (GP clinic)	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Community nurse	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Health visitor	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Psychologist	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Counsellor	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Physiotherapist	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Occupational health therapist	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Care manager	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Social worker	☐☐	☐☐	☐	☐	☐	☐	☐☐☐

Service	Number of home visits	Number of visits to surgery or clinic	Provider agency (please tick)				Average duration of contact (minutes)
			NHS	Local authority	Voluntary organisation	Private organisation	
Home care worker	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Care attendant	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Sitting scheme	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Carer's support worker	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Chiropodist	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Dietician	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Self-help group	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Meals on wheels	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Laundry service	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
Other: e.g. dentist, optician, alternative medicine / therapist							
1.	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
2.	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
3.	☐☐	☐☐	☐	☐	☐	☐	☐☐☐
4.	☐☐	☐☐	☐	☐	☐	☐	☐☐☐

Appendix F: WHO PERFORMANCE STATUS

0 Able to carry out all normal activity without restriction.

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

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

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

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

Appendix G: PET/CT PROTOCOL

1 Patients

- Patients with diabetes mellitus either type 1 or type 2 must be well controlled with a fasting blood glucose not exceeding 10.0mmol/l.
- Specific guidelines for patients with either type 1 or type 2 diabetes mellitus as follows;

Type 1 - **insulin dependent diabetes mellitus (requires injections) and Type 2** - **diabetes mellitus (requires oral anti-diabetic drugs such as Metformin or pioglitazone)**

Arrange for the patient to have an appointment at 12 midday where practicably possible

- Instruct patient to eat breakfast at 6am and have their normal dose of Insulin/medication at this time, and then only drink water.
- The patient should not have any more insulin/diabetes medication until after the scan.
- Instruct patient to bring something with them to eat straight after the scan.
- Instruct patient to bring their insulin/diabetes medication with them.
- Instruct patient to bring any emergency medication they have been issued with.
- If a midday appointment cannot be arranged then instruct the patient to eat and take insulin/medication 6 hours prior to the appointment time.
- Do not encourage the patient to starve for more than 6 hours prior to the appointment

Type 2 - **diabetes mellitus controlled by diet**

- Determine from patient when their blood sugar level is normally lowest. Book the appointment at this time if possible.
- Instruct the patient to eat 6 hours prior to the appointment time and then starve and just drink water until after their appointment.
- Instruct the patient to bring something with them to eat straight after the scan.

2 Preparation:

- Patients to fast for 6 hours prior to scan.
- Patients weighed without shoes and coats (ensure calibrated class III device with requirements defined in the Non-Automatic Weighing Instruments Directive 2003).
- Blood glucose monitored using BM Glucometer (ensure calibrated device).
- Patients to drink 2-3 glasses of water prior to test to ensure hydration**.**
- Metal denture fixtures etc to be removed whenever possible (CT artefacts).

3 Injection:

- FDG injected via butterfly cannula under quiet conditions.
- Patient to remain silent.
- FOR 2D scanning inject 350-530MBq. Important must ask the ARSAC holder for approval above 400MBq (ARSAC DRL) for any patients.
- FOR 3D scanning inject 150-350MBq
-
- Measure syringe residue and reduce injected activity accordingly.

4 Uptake:

- Patient to remain quiet and inactive during uptake at room temp.
- Patient to empty bladder just prior to positioning on scanner bed.
- Emission scan must start at 90 minutes post injection.

5 Positioning:

- Patient to be scanned on regular couch top.
- Begin scanning at the groin and end at the base of the orbits.
- Scan with arms up if a single whole body scan is performed.

6 Acquisition Parameters:

- Use routine local protocols

7 Reconstruction Parameters:

- OSEM with CT for attenuation correction using local routine parameters.

8 Local Archive

- Reconstructed CT, PET AC and PET NAC data MUST be archived locally. Raw data to be archived according to local protocol.

9 Quality Assurance and Control:

- Under agreed QA and QC protocols using suitable phantom and anonymised test patient scans etc.
- Ensure accurate SUV are recorded for study

10 PET/CT data transfer to the Core Lab:

Under agreed protocol transfer following reconstructed and anonymised files

- CT
- PET AC
- PET NAC
- PET/CT report from local imaging team

11 Local reporting of PET/CT

- A report will be made by the imaging team in the local hospital. The image data together with the report will be transferred to the central laboratory using agreed protocols.
- Local and central reports as a minimum requirement shall asses the following with SUV max values quoted where applicable;
  - Pancreatic lesion
  - Lymph nodes
  - Metastases
  - Synchronous lesions
- PET/CT will be reviewed by an expert in clinical PET/CT, independent of the report from the local hospital.

- Any differences between the local hospital and the central laboratory will be resolved by consensus with the local hospital team.
- Standardised criterion will be used for reporting the scans.

12 Data Transfer to Core Lab

- Procedures must be in place to ensure image data is sent to the PET/CT Core Lab promptly to allow central reporting to fit in with any patient treatment schedules.

- All image files must be compliant with DICOM PART 10 format.

- An agreed, tested and secure method must be used to transfer anonymised data between scanning facilities and the PET/CT Core Lab.

- All files must be clearly named using a pre-arranged filename convention

- Named persons (and their deputies) should be identified with responsibility for scanning, QC and data transfer at participating PET/CT centres.

- For each patient study data acquisition information and patient information must be recorded and forwarded under agreed protocols to the PET/CT Core Lab at the same time as the image data is transferred.

Appendix H: UICC 7th Edition, 2009 (pancreas section extract)

Pancreas
(ICD-O C25)

Rules for Classification

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

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

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

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

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

Anatomical Subsites

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

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

Regional Lymph Nodes

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

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

TNM Clinical Classification

T - Primary Tumour

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

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

N - Regional Lymph Nodes

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

M - Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

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

pTNM Pathological Classification

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

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

pM – Distant Metastasis*

pM1 Distant metastasis microscopically confirmed

Note: *pM0 and pMX are not valid categories

Residual Tumour (R) Classification*

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

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

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

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

G Histopathological Grading

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

Stage Grouping

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

Summary

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

Appendix I: EQ-5D Health Questionnaire (English version for the UK) Script for telephone administration.

Health Questionnaire

(English version for the UK)

SCRIPT FOR TELEPHONE ADMINISTRATION

GENERAL INTRODUCTION

It is suggested that the telephone administrator follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on page 2, the precise wording must be followed.

It is recommended that the administrator has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the administrator on behalf of the respondent (i.e. the appropriate boxes on page 2 are marked and the scale on page 3 is marked at the point indicating the respondents 'own health state today'). If the respondent asks for clarification, the administrator can help by re-reading the question verbatim. The administrator should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty with regard to which box to mark, the administrator should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health state today.

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INTRODUCTION TO EQ-5D

We are trying to find out what you think about your health. I will first ask you a few brief and simple questions about your own health state today. I will then ask you to do a rather different task that involves rating your health on a measuring scale. I will explain the tasks fully as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM - PAGE 2: INTRODUCTION

First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state today.

Do not choose more than one answer in each group of questions.

(Note for administrator: it may be necessary to remind the respondent regularly that the timeframe is today.)

EQ-5D DESCRIPTIVE SYSTEM - PAGE 2: TASK

MOBILITY

First I'd like to ask you about mobility.

Question 1: Would you say you have…

1. **No problems in walking about?**
2. **Some problems in walking about?**
3. **Are you confined to bed?**

So, would you say you have no problems in walking about, some problems in walking about or are you confined to bed?

(Note for administrator: mark the appropriate box on EQ-5D)

SELF-CARE

Next I'd like to ask you about self-care.

Question 2: Would you say you have…

1. **No problems with self-care?**
2. **Some problems washing or dressing yourself?**
3. **Are you unable to wash or dress yourself?**

So, would you say you have no problems with self-care, some problems washing or dressing yourself or are you unable to wash or dress yourself?

(Note for administrator: mark the appropriate box on EQ-5D)

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USUAL ACTIVITIES

Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities.

Question 3: Would you say you have…

1. **No problems with performing your usual activities?**
2. **Some problems with performing your usual activities?**
3. **Are you unable to perform your usual activities?**

So, would you say you have no problems with performing your usual activities, some problems with performing your usual activities or are you unable to perform your usual activities?

(Note for administrator: mark the appropriate box on EQ-5D)

PAIN/DISCOMFORT

Next I'd like to ask you about pain or discomfort.

Question 4: Would you say you have…

1. **No pain or discomfort?**
2. **Moderate pain or discomfort?**
3. **Extreme pain or discomfort?**

So, would you say you have no pain or discomfort, moderate pain or discomfort or extreme pain or discomfort?

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY/DEPRESSION

Finally I'd like to ask you about anxiety or depression.

Question 5: Would you say you are…

1. **Not anxious or depressed?**
2. **Moderately anxious or depressed?**
3. **Extremely anxious or depressed?**

So, would you say you are not anxious or depressed, moderately anxious or depressed or extremely anxious or depressed?

(Note for administrator: mark the appropriate box on the EQ-5D questionnaire)

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EQ VAS - PAGE 3: INTRODUCTION

(Note for administrator: If possible, it might be useful to send a visual aid (i.e. the EQ VAS) before the telephone call so that they can have this in front of them when completing the task).

I would now like to ask you to do a rather different task.

To help you say how good or bad your health state is, I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health state you can imagine is marked 100 (one hundred) at the top of the scale and the worst state you can imagine is marked 0 (zero) at the bottom.

EQ VAS - PAGE 3: TASK

I would now like you to tell me the point on this scale where you would put your own health state today.

Thank you for taking the time to answer these questions.

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