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# View application from Keith Roberts

Created: 31 Jan 2020, 9:31 a.m.

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## Abstract

<b>Title of Study</b>	PARANOIA: The Pancreatic Anastomosis Audit
<b>Abstract and methodological description</b>	<p><b>Aim:</b> To develop a stable platform for the routine collection of factors that may relate to post operative pancreatic fistula development. The database will permit analysis of risk factors, provide users risk adjusted CUSUM outcomes and will be used to implement Trials Within a Cohort Studies.</p> <p><b>Introduction</b></p> <p>Post-operative pancreatic fistula (POPF) is the main cause of morbidity and mortality after pancreatic surgery. Clinically relevant POPF affects around 15% of patients. Given the frequency of POPF and its complications, it is associated with a large financial burden where its occurrence doubles healthcare costs. There are many known risk factors and several risk scores. Many trials seek to reduce fistula occurrence but many suffer methodological flaws. The creation of a POPF registry could overcome geographic barriers, enable a better understanding of POPF risk and identify previously 'unknown' risk factors. It will provide users with risk adjusted CUSUM plots to allow self assessment and help inform and design future studies.</p> <p><b>Methods:</b> A twelve-month international multicentre prospective audit will be performed starting in late 2020 and co-ordinated by PARANOIA, a team from the West Midlands Research Collaborative. Patients</p>



undergoing pancreaticoduodenectomy over 12 months with a 90-day follow up period. A pilot test will occur at five specialist sites in mid 2020.

Audit standards assessed:

- expected POPF rate (ISGPS grades B or C) 15%;
- major post-operative morbidity (Clavien Dindo Grade III/+) 15%.
- 30-day mortality rate < 5%
- 90-day mortality rate < 8%.

Conclusion: This will be a trainee led international audit of pancreaticoduodenectomy practice. Key support will be given by consultant colleagues and patient representatives. Individualised unit and surgeon data will be distributed confidentially to the respective contributing sites and surgeons.

Anonymised and pooled results of audit will be published in peer reviewed journals with all collaborators acknowledged. Key information and results from the audit will be disseminated at relevant scientific meetings.

Importance and potential of the work

Despite advances in technology and healthcare post-operative pancreatic fistula (POPF) remains the single largest problem of pancreatic surgery. It is dependent upon patient and surgeon factors and as such many studies have sought to understand and limit its impact. Whilst understanding has improved there are numerous inconsistencies throughout the literature in terms of understanding risk and studies are largely negative i.e. fail to demonstrate benefit of the tested intervention.

The approach of single site or traditional randomised surgical trials are fundamentally flawed for a multitude of reasons, from the complexity of pancreaticoduodenectomy to the processes within trials. Multinational audits of surgical anastomosis (e.g. oesophagogastric and colorectal) have demonstrated the ability to capture data on thousands of patients overcoming geographic and methodological flaws associated with more traditional studies.

Thus, establishing a stable platform for the routine audit of POPF is highly attractive. This method can determine the accuracy of established risk scores and factors measured across the world in a short period which limits confounding due to changes in practice over time or surgical technique due to the increased power that comes with very large numbers of patients.

Furthermore, an individual's risk varies of POPF varies widely and thus providing users with their own risk adjusted CUSUM plots takes into account this variation and provides the user with real time assessment of their surgical performance. This is an entirely novel approach and itself will form the basis for study of the impact of providing this information within future sub-studies.

By establishing this platform we will provide a system for the ongoing assessment of POPF. Learning through better understanding of risk factors, feedback through CUSUM and interventions, trials and sub-studies during the lifetime of the audit will directly influence practice, the outcomes of which will be measured by repeated audit to assess global impact.

#### Aim

To establish a stable platform for the routine collection of variables relating to POPF. In the first instance we will run a preliminary audit of POPF to determine feasibility, user acceptability before leading to a global audit of POPF which will also answer relevant research questions. This will be used to validate the proposed platform and method.

Key points in the delivery of this project

1. Determine which factors to include with the database through systematic review and meta-analysis
2. Develop the database for the routine collection of variables using the REDCap secure web application in conjunction with the Birmingham Surgical Trials Consortium. REDCap is designed to support data capture for research studies.
3. Quantify the incidence of POPF rate across an international multicentre audit to assess variation in observed incidence
4. Compare the accuracy of published risk scores to predict POPF among this international dataset (key research outcome)
5. Provide users with their own risk adjusted CUSUM plots and to define characteristics of surgeons, stratified by the rate of observed-expected POPF to determine whether experience and other surgical factors relate to POPF (secondary key research outcome). This analysis will include the impact of centralisation and volume of pancreatic services and high, middle- and low-income countries upon POPF rates

Throughout the development and implementation phase, meetings will be held with key stakeholders to develop the strategy, report data and plan for future work.

### Methodology

Our group have performed several systematic reviews and meta-analyses which has informed the dataset and primary objectives; these are summarised here with abstracts available on request:

1. A meta-analysis of 122 studies including over 52,000 patients looked at factors associated with POPF following pancreatic resections, demonstrated variation in reported rates of POPF and risk factors. This highlighted heterogeneity between studies raising concerns over the generalisability of published data and that factors associated with all-POPF or CR-POPF were not consistent.
2. A systematic review identified 25 published scoring systems for POPF but only 4 could be assessed by external validation highlighting the problem of lack of suitable validation. Among tested scores all performed well (AUROC 0.68-0.73) but high levels of heterogeneity suggest a score that works consistently across geographical and organisational barriers is needed
3. The fear of morbidity, particularly POPF, can be a barrier to surgical trainees gaining vital experience. This meta-analysis sought to establish the POPF rate following PD by trainees or established surgeons. 3 of 53 studies were included for meta-analysis, all defining POPF using ISGPS 2005 criteria. Some 309 PD (16%) were performed by trainees. The rate of POPF after surgery performed by those who had completed training was not different when surgery was performed by trainees nor mortality or delayed gastric emptying. PD, when performed by trainees, is associated with acceptable outcomes. Evidence of heterogeneity in key variables indicates a need for further studies and it is unclear whether outcomes are similar when trainees perform surgery among patients stratified as low or high risk for POPF using established risk scores. The use of risk adjusted CUSUM as reported recently could be a useful tool to assess trainee's performance.
4. A meta-analysis to identify and evaluate the effect of interventions upon POPF was performed. 56 studies of 20 different interventions were identified with just four being amenable to meta-analysis which

significantly reduced the rate of POPF: external pancreatic stent compared to no stent; invagination pancreaticojejunostomy (PJ) compared to duct to mucosa; pancreaticogastrostomy (PG) compared to PJ and omission of intraabdominal drains in patients with low risk PJ anastomoses. However, high heterogeneity between studies and inconsistent results however suggest that novel methodological approaches to determining benefit, particularly of surgical techniques, are required.

#### Study Period

A global prospective audit of patients undergoing pancreatoduodenectomy over a 12-month period (October 2020-2021) with 90 day follow-up after surgical resection. No additional patient follow-up or intervention is required that would deviate from the normal patient journey. Data would be collated from electronic and paper records. Registered units must include consecutive patients undergoing pancreatoduodenectomy during the study period. A 2-month pilot of 5 centres (UK/international), will be undertaken to finalise the detailed online case report forms.

#### Study Population

##### Inclusion Criteria

- All adult patients undergoing pancreatoduodenectomy for any indication
- Any approach (open, robotic, laparoscopic)

##### Exclusion criteria

- Age <18y

Patient identification- any combination of

- Multidisciplinary team meetings
- Coordination with lead surgeon and HPB Specialist nursing services
- Review of theatre lists

##### Centre Eligibility

Any centre routinely performing pancreatic resections is eligible. No restriction will be placed on global location or number of surgeons involved.

Each unit will be required to:

- register prior to the start date for data collection.
- responsible for obtaining local hospital approval
- ensure >95% completeness of data entry before the study closes.

##### Data Completion and Organisation

Data input will be via a dedicated encrypted server through the Research Electronic Data Capture (REDCap) web application. No patient identifiable

information will be inputted into the database. Locally held records containing corresponding REDCap ID numbers and local patient identifiers must be stored securely.

Patient data will be entered into case report forms (CRFs) which are designed not to deviate from safe patient care. Each unit will have a lead auditor of Consultant grade. Units with >5% missing data will be excluded. The Birmingham Surgical Trials Consortium, will host the REDCap system. All data will be stored securely on encrypted and certified servers for a minimum of 5 years.

A 2-month pilot of 5 centres will be undertaken to finalise the detailed online CRF to ensure all relevant data is collected to achieve the goals of the audit.

Research environment and people

PARANOIA is an international multicentre study run on behalf of the West Midlands Research Collaborative (WMRC). For over a decade WMRC has an excellent track record for successfully delivering high quality clinical research including three multicentre RCTs, five observational cohort studies and 43 publications to date. In particular, RICOCHET (Receipt of Curative resection Or palliative Care for HEpato-pancreato-biliary Tumours) was a national audit designed to map the pathway of patients with malignant obstructive jaundice from secondary to tertiary care. Each UK centre participating in RICOCHET is familiar with the REDCap system and has shown enthusiasm for collaborative work.

This ambitious project is led by a team of experienced trainees and supported by consultants invested in propelling research into pancreatic cancer.

Keith Roberts is the Pancreas Surgery Speciality Lead for the Royal College of Surgeons, honorary treasurer to the Pancreatic Society of Great Britain and Ireland and medical advisor to Pancreatic Cancer UK.

Through these roles he is able to help understand the need of pancreatic cancer patients and disseminate the results of research to maximise their impact.

Professor Pinkney is Clinical Director of the Birmingham Surgical Trials Consortium. As a founding member of the West Midlands Research Collaborative, he maintains an interest in development of trainee-led clinical trials in surgery.

Professor Bobby Tingstedt is the Chairman for the National Guidelines Group for Pancreatic Cancer and for the Swedish Cancer registry for Pancreatic cancer.

Rupaly Pande is a research registrar at the liver unit in Birmingham conducting her PhD on development of devices to improve outcomes after pancreatic surgery, particularly through understanding and reducing POPF. She is on the steering committee for RICOCHET and IMPROVEPanc.

Francesco Giovinazzo is a senior fellow at the liver unit in Birmingham with vast experience in the field and Co-editor in Chief at Frontiers of Surgical Oncology.

Samir Pathak is an Academic Clinical Lecturer in HPB and General Surgery in Bristol and Associate Speciality Lead for the RCS. He is on the steering committee for SUNFLOWER and area of interest is innovation into HPB surgery.

Stephen Knight is NIHR Clinical Research Fellow at Edinburgh on the steering committee for GlobalSurg3. He is undertaking a PhD based in Global Surgery and mobile technology to measure surgical outcomes.

Sivesh Kamarajah is an academic foundation year doctor in Newcastle on the steering committees for collaborative studies such as OGAA, GlobalSurg and STARSurg.

James Skipworth and Ali Arshad are both consultant HPB surgeons committed to supporting trainees and developing collaborative projects in HPB.

Rita Perry and Laura Magill run the unit for prospective non-randomised surgical studies at University of Birmingham and have significant experience and expertise of delivering similar REDCap-based projects on an international scale.

## Timetable

<b>Name</b>	Derivation of dataset
<b>Date</b>	01/03/2020

<b>Name</b>	Feasibility test at 5 sites
<b>Date</b>	01/04/2020

<b>Name</b>	1-day meeting at RCS to discuss results of systematic reviews, results from the feasibility test and hear from other groups such as oesophagogastric and colorectal studies of anastomotic leak
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<b>Date</b>	01/07/2020
<b>Name</b>	International audit of POPF
<b>Date</b>	01/10/2020

## Funding

<b>Name</b>	Data manager (Band 6) at 0.25% FEC (no overheads), for 12 months
<b>Amount</b>	9100.0

<b>Name</b>	Contribution to statistician costs
<b>Amount</b>	900.0

## Details of ethical approval

PARANOIA has been discussed with the local Research and Development department at University Hospitals of Birmingham and is registered as an audit (CARMS-15831). Therefore, ethics approval will not be required, HRA decision tool available on request.

## Institutional approval information

Not applicable as this is a registered audit.

## Declaration

Confirm Declaration: No

Head of Department

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# View application from MOHAMED EYAD ISSA

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Created: 29 Jan 2020, 9:45 p.m.

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## Abstract

<b>Title of Study</b>	Can multiplex deep sequencing of circulating free DNA detect pancreatic cancer at an early stage?
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<b>Abstract and methodological description</b>	<p><b>Aims:</b></p> <p>The detection of circulating tumour-derived biomarkers in blood could provide a non-invasive approach for the early detection of pancreatic ductal adenocarcinoma (PDAC). The aim of this study is to provide “proof of principle” that point mutations in key cancer genes can be identified by sequencing of circulating free DNA (cfDNA) isolated from blood plasma. With appropriate validation cfDNA levels could detect a significant number of early PDACs and potentially premalignant lesions, helping to target early effective treatment.</p> <p><b>Objectives:</b></p> <p>Collection of patient samples: We have already collected blood samples and fresh tumour tissues from patients with resectable and non-resectable PDAC (12). Further peripheral and central blood samples as well as fresh tumour tissues will be collected under existing ethical approval.</p> <p>Sequencing: We will test the feasibility of multiplex cfDNA sequencing in 10 patients with non-resectable PDAC, and then compare those results to 10 patients with resectable disease. Data from these 2 cohorts will be compared with 10 healthy age-matched volunteers by bioinformatic analyses.</p> <p>Comparison between tumour and cfDNA: We hypothesise that driver mutations will be present in both cfDNA and the primary tumour, but other mutations acquired as the disease progresses may be unique to cfDNA. Therefore, we will analyse matched primary tumour samples from 10-20 patients with PDAC for mutations detected in cfDNA.</p>
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## Timetable

<b>Name</b>	1: Initial analyses of non-resectable patient samples to establish the technique for PDAC
<b>Date</b>	01/03/2020-30/06/2020
<b>Name</b>	2: Patient and volunteer recruitment/sample collection and preparation
<b>Date</b>	01/03/2020-30/10/2020
<b>Name</b>	3: Analysis of cfDNA genotypes

<b>Date</b>	01/03/2020-28/02/2021
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<b>Name</b>	4. Comparison of cfDNA and tumour tissue
<b>Date</b>	01/09/2020-28/02/2021

<b>Name</b>	5. Data analysis
<b>Date</b>	01/03/2020-28/02/2021

## Funding

<b>Name</b>	Sequencing using the Pan-Cancer panel
<b>Amount</b>	9560.0

## Details of ethical approval

The Study is currently taking place under the ExPAT ethical approval study number: UNOLE0472.

## Institutional approval information

The application has the approval of the Head of department and the finical officer.

## Declaration

Confirm Declaration: Yes

### Head of Department

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# View application from Mustafa Jalal

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Created: 4 Dec 2019, 4:01 p.m.

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## Abstract

<b>Title of Study</b>	Computerised tomography quantification of sarcopenia in chronic pancreatitis using digital analysis, a case controlled study
<b>Abstract and methodological description</b>	<p>Abstract</p> <p>Chronic pancreatitis (CP) is an irreversible, progressive condition where scarring of the pancreas occurs in response to inflammation. It presents with upper abdominal pain and malnutrition. Recognition of CP can be challenging especially in its early stages and patients require nutritional assessment and support as part of their multidisciplinary management. Early non-age related loss of skeletal muscle mass, known as secondary sarcopenia, is a marker of malnutrition. Sarcopenia causes muscle function loss and increasing frailty and has been shown to be associated with a poor prognosis in patients in medical, surgical and oncological studies. Skeletal muscle mass can be assessed in numerous ways including hand grip strength but more recently computerised tomography (CT) has been used for a more standardised approach. Software has now also been validated to further increase the standardization of skeletal muscle assessment on CT and look for sarcopenia. Given most patients with a diagnosis of CP undergo a CT scan, using this software could make a rapid, early, objective assessment of nutritional status. This would allow the opportunity to deliver early intensive nutritional support and potentially improve outcomes.</p> <p>We aim to assess the prevalence and severity of sarcopenia in patients with chronic pancreatitis and</p>

their nutritional status using skeletal muscle recognition software. We plan to undertake the analysis in patients that are being recruited to a current ethically approved study of patients undergoing endoscopic ultrasound. This group of patients have already had a CT and been given a diagnosis of chronic pancreatitis – hence the referral for endoscopic ultrasound. We also have a control group of patients with no evidence of CP and a CT undertaken for other clinical indications.

#### Aim of the study

Primary aim: To assess the prevalence and severity of sarcopenia in patients with chronic pancreatitis and their nutritional status using skeletal muscle recognition software

Secondary Aim: To compare the level of sarcopenia between patients with chronic pancreatitis and those without using skeletal recognition software

#### Background

Chronic pancreatitis (CP) is an irreversible, progressive condition where scarring of the pancreas occurs in response to inflammation from many aetiologies. It presents with relapsing, remitting upper abdominal pain accompanied by features of malabsorption and malnutrition due to pain and pancreatic exocrine insufficiency (PEI) and endocrine deficiency with diabetes. Recognition of CP can be challenging especially in its early stages and patients require multidisciplinary management with early intervention to prevent complications developing. PEI, anorexia secondary to abdominal pain, nausea and vomiting, alcohol and diabetes mellitus may all contribute to malnutrition in patients with CP. Current European nutrition and pancreatic guidelines suggest using the community Malnutrition Universal Screening (MUST) tool to assess patients with CP. Two prospective studies of 58 and 62 patients with CP have shown a significant decrease in the lean muscle mass and body fat compared to controls recognising the need for full nutritional assessment. (1,2).

Sarcopenia is defined as the loss of muscle protein mass which in turn results in loss of muscle strength and a decline in functional quality (3). Sarcopenia can have an impact on quality of life and maybe associated with osteoporosis. Loss of muscle mass by other causes rather than ageing is termed secondary sarcopenia (4). Sarcopenia is independent of body mass index (BMI) used by the MUST tool and can be present in underweight and overweight patients.



Sarcopenia causes muscle function loss and increasing frailty, and has been shown to be associated with a poor prognosis in patients in medical, surgical and oncological studies particularly pancreatic cancer (5). Skeletal muscle mass can be assessed in numerous ways, including hand grip strength, but more recently computerised tomography has been used for a more standardised approach. Software has now also been validated to increase the standardization of skeletal muscle assessment on CT and look for sarcopenia (6).

Sarcopenia has been shown to be strongly associated with pancreatic exocrine insufficiency PEI(7), however the prevalence in CP has only been currently reported in 2 abstracts only using digital CT. Retrospective assessment of known patients with CP (both which used 29 patients) showed the prevalence of sarcopenia to be 52-62% (8, 9). Given most patients with CP undergo a CT scan, CT quantification rates of sarcopenia using digital analysis software could make a rapid, early, objective assessment of nutritional status. This would allow the opportunity to deliver early nutritional support and avoid poor outcomes seen in other conditions.

#### Methodology:

We are currently undertaking ongoing recruitment for a prospective ethically approved study: 'Elastography in the diagnosis of chronic pancreatitis' IRAS210710 STH19471, hypothesising that early changes of chronic pancreatitis can be detected using elastography assisted Endoscopic ultrasound (EUS). Recent early results have been published with further recruitment planned for a further year (10).

Those undergoing a full pancreas assessment due to tests suggestive of chronic pancreatitis or those with unexplained abdominal pain are identified for study inclusion. Data from the patients' current investigations will be used to identify the suspected presence of chronic pancreatitis which have already included a CT scan.

#### Current Inclusion criteria for study:

Age 18 or over, Patients referred for EUS for investigation of abdominal pain without a cause found on assessment with CT and FEL-1 (control group) & Patients referred for EUS for chronic pancreatitis assessment based on CT and FEL-1 testing.

Exclusion criteria for the study group include Patients with known solid pancreatic lesions; Patients under the age of 18; Patients who decline EUS

examination; Patients referred for EUS with indications other than epigastric pain or suspicion of chronic pancreatitis; Patient without a CT scan or with significant artifact seen at the 3rd lumbar vertebrae (L3) level.

To reach the desired sample size we require a further 50 patients in each arm. We aim to continue the recruitment with an ethical amendment to allow skeletal muscle assessment of the patients CT scan recruited into the study.

#### Design

Patients prospectively recruited into the study will have the CT images examined. A single axial CT-image at the level of the third lumbar vertebrae (L3) will be assessed. All patient data will be removed and a single patient study number will be assigned to the image. Images will be analyzed using commercially available software (Slice-O-Matic V5, Tomovision). A single axial CT-image at the level of the third lumbar vertebrae will be assessed to measure cross-sectional areas (cm<sup>2</sup>) of skeletal muscle (psoas major, erector spinae, quadratus lumborum, and abdominis muscles).

ABACS is an add-on software and requires SliceOmatic in order to function. It automatically identifies, paints and measures skeletal muscle area. It also provides measurement of subcutaneous adipose tissue, visceral adipose tissue and intramuscular fat infiltration. It is capable of analysing large number of scans within short time. The study can be undertaken using SliceOmatic only but ABACS will reduce intra-observer variability and increase efficiency

The surface areas value will be normalized for the height of the patient to get the lumbar skeletal muscle index (L3 SMI) in cm<sup>2</sup>/m<sup>2</sup>. The sex-specific sarcopenia cut-offs are 52.4 cm<sup>2</sup>/m<sup>2</sup> for men and 38.5 cm<sup>2</sup>/m<sup>2</sup> for women (11). Results will be identified and data collected prospectively. There is no randomization but blinding of the presence of CT changes of pancreatitis is possible as the pancreas will not be seen in the L3 image used for the skeletal muscle assessment. Patients recruited into the study have already had pancreatic assessment for CP with CT/MRI and EUS assessment (Rosemont criteria). BMI and alcohol and smoking and nutritional history is recorded as part of the existing study also.

#### Sample size

Given the previously reported prevalence of

sarcopenia in CP and differences seen<sup>5,8,9</sup>. The sample size of this study will be set at minimum 34 (>17 with CP). A 1:1 enrolment ratio was used, alpha 0.05, power 90%. By analyzing previous recruitment this number would be recruited in 6-12 months.

#### Setting

The project will be carried out on the clinical investigation unit at the Royal Hallamshire Hospital, Sheffield.

#### Participants

The study will be undertaken by a single centre: Royal Hallamshire Hospital, Sheffield Teaching Hospitals. Patients identified from gastroenterology and surgical clinics referred for EUS and recruited for the 'Elastography in the diagnosis of chronic pancreatitis' study with CT imaging available at the L3 level.

#### Outcome measure

Prevalence of sarcopenia and muscle mass measurement in patients with chronic pancreatitis compared to control group.

#### Ethical issues

No ethical issues are identified. Patients will already have been managed by the clinical care team according to the findings of EUS or CT scans. Given lack of evidence and early reporting of the software results of the CT scan sarcopenia analysis will not be used to alter patient care. There is no risk identified. Patients' rights, privacy and confidentiality are respected. No additional identifiable patient information is required. Analysis of results will be stored on a password protected hospital computer.

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## Timetable

<b>Name</b>	Patient recruitment
<b>Date</b>	April-December 2020

<b>Name</b>	SliceOmatic measurement
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<b>Date</b>	January 2021
<b>Name</b>	Data analysis and writing up
<b>Date</b>	February 2021
<b>Name</b>	Dissminaiotn
<b>Date</b>	June 2021

## Funding

<b>Name</b>	Purchase of sliceOmatic software- including 10% academic discount. 1GBP=1.28 USD as of 4 Dec 2019
<b>Amount</b>	2855.0
<b>Name</b>	Purchase of ABACS (Voroni Health analytics)- including 10% academic discount
<b>Amount</b>	1410.0
<b>Name</b>	Total in GBP
<b>Amount</b>	4265.0

## Details of ethical approval

We obtained approval to addendum to previous ethical approval for study: 'Elastography in the diagnosis of chronic pancreatitis' IRAS210710 STH19471.

## Institutional approval information

This application has been approved by the Head of Department.

## Declaration

Confirm Declaration: Yes

Head of Department

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# View application from Giuseppe Garcea

Created: 29 Jan 2020, 5 p.m.

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## Institution Details

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## Abstract

<b>Title of Study</b>	RANDOMISED DOUBLE BLINDED CONTROLLED TRIAL OF SINGLE DOSE INTRAOPERATIVE HIGH-DOSE STEROIDS AND OUTCOMES FROM PANCREATIC HEAD RESECTIONS
<b>Abstract and methodological description</b>	<p>RANDOMISED DOUBLE BLINDED CONTROLLED TRIAL OF SINGLE DOSE INTRAOPERATIVE HIGH-DOSE STEROIDS AND OUTCOMES FROM PANCREATIC HEAD RESECTIONS</p> <p>ABSTRACT</p> <p>Background:</p> <p>There is limited but significant evidence that intraoperative steroids can attenuate the inflammatory response from surgery which in turn, can result in decreased post-operative complications. Currently, only one randomised controlled trial has examined the impact of steroids following pancreatic resection. This</p>



study will examine the impact of high dose intraoperative steroids on a range of factors such length of stay, morbidity, inflammatory response (via circulating IL-6 and TNF-alpha levels), resumption of oral nutrition and visual analogue scores (VAS) for pain control, nausea and fatigue after pancreaticoduodenectomy.

#### Methods:

Randomised controlled double-blinded study. The treatment arm will receive 100mg of intraoperative dexamethasone 20mg on induction or normal saline placebo. Primary outcome measures include morbidity (assessed by the Clavien-Dindo system), 30 and 90 Day mortality, High Dependency Unit length of stay, overall length of stay, C reactive protein levels (days 0, 1, 3, 5 and 10 post-operatively), Visual analogue pain scores (VAS), (days 0, 1, 3, 5 and 10 post-operatively), (days 0, 1, 3, 5 and 10 post-operatively), anastomotic leak rates and grade (ISGPS grading), serum amylase (days 0, 1, 3, 5 and 10 post-operatively), drain amylase (days 1, 3, 5 and 10 post-operatively), patient controlled analgesia opiate consumption (converted to opiate equivalent units), oral opiate consumption (converted to opiate equivalent units), resumption of oral nutrition and evidence of delayed gastric emptying (ISGPS definition). Attenuation of an inflammatory response will be assessed with ELISA assays of IL-6 and TNF-alpha on days 0, 1, 3, 5 and 10.

#### Results:

All data entry will be verified by the main researcher. Statistical analyses planned will be  $\chi^2$  test and Fisher's exact probability test for categorical data. Student's t-test will be used for comparisons between time points and for comparisons between groups at a particular time point; equal variances will not be assumed. Analysis of variance (ANOVA) will be used to analyse the effects of steroids on the overall results, effect of time factor (time points) on the overall results in both groups and to determine if there is any interaction between both groups. In all cases, a value of  $P < 0.05$  will be taken to indicate statistical significance. Data will be presented as mean  $\pm$  SEM.

#### BACKGROUND:

There is increasing evidence that intraoperative steroids can ameliorate the systemic response following major surgery. Benefits for gastrointestinal surgery include a reduction in post-operative nausea, shivering, improved recovery satisfaction scores (1).

Other benefits include a reduction in post-operative pain scores, reduction in opioid usage (2), a reduction in post-operative delirium (3) improvement in mobility (4) and a reduced length of stay (LoS) (5). These positive associations have been observed in a range of different surgeries from intra-abdominal procedures, thoracic surgery, cardiac surgery and orthopaedic surgery. No published study, thus far, has documented an increase in steroid-related post-operative complications (5,6).

In HPB surgery, there is a paucity of data regarding efficacy of intraoperative steroids. Evidence from the use of steroids during liver resection suggests that steroids may reduce the degree of liver dysfunction post-operatively (7) and that steroids in the post-operative period may encourage faster normalisation of liver function tests (8). In pancreatic resections, one single study has demonstrated that steroids reduced the risk of major complications in high-risk patients from 41 to 18% (9). Other work in pancreatic surgery has demonstrated that delayed gastric emptying (DGE) is an inflammatory associated consequence secondary to circulating IL-6 levels (10); making DGE a potential target for steroid administration.

These early results strongly suggest that the use of high-dose intraoperative steroids requires further evaluation in pancreatic surgery. The potential beneficial effects include a reduced risk of major complications, reduced DGE, reduced nausea, reduced post-operative delirium, reduced LoS and improved patient satisfaction. There is currently no evidence that the single-use steroids significantly increases post-operative risk or increases cancer recurrence risk (11).

#### HYPOTHESIS:

Single shot high-dose steroids administered intra-operatively offer beneficial effects in patients undergoing pancreatic resections (due to attenuation of the inflammatory response associated with surgery) with no increase in morbidity or mortality.

#### PRIMARY OUTCOME MEASURES:

Primary outcome measures include-

- Morbidity (assessed by the Clavien-Dindo system)
- 30 and 90 Day mortality
- High Dependency Unit length of stay
- TNF-alpha and IL-6 serum levels on days 0, 1, 3, 5, and 10 post-operatively

- Overall length of stay
- C reactive protein levels days 0, 1, 3, 5 and 10 post-operatively
- Visual analogue pain scores (VAS) days 0, 1, 3, 5 and 10 post-operatively
- Nausea and vomiting scores (VAS) days 0, 1, 3, 5 and 10 post-operatively
- Anastomotic leak rates and grade, defined by Bassi et al (12)
- Serum amylase days 0, 1, 3, 5 and 10 post-operatively
- Drain amylase on days 1, 3, 5 and 10 post-operatively
- Patient controlled analgesia opiate consumption days 0, 1, 3, 5, and 10 (converted to opiate equivalent units)
- Oral opiate consumption, days 0, 1, 3, 5, and 10 (converted to opiate equivalent units)
- Resumption of oral nutrition and evidence of delayed gastric emptying as defined by the ISGPS (13)

#### SECONDARY OUTCOME MEASURES:

Secondary outcome measures include-

- QOR-40 validated questionnaires for post-operative recovery day 1 and day
- Time to mobilise (days)
- Fatigue levels (VAS), days 0, 1, 3, 5 and 10 post-operatively
- 4-AT delirium score at days 0, 1 and 5 post-operatively
- Neutrophil to lymphocyte ratio on days 0, 1, 3, 5 and 10 post-operatively
- Platelet to lymphocyte ratio on days 0, 1, 3, 5, and 10 post-operatively

#### INCLUSION/EXCLUSION CRITERIA:

##### INCLUSION CRITERIA

- All patients with a radiological or histological diagnosis of periampullary cancer.
- Patients undergoing resection of their periampullary cancer

##### EXCLUSION CRITERIA

- Patients unable to consent to study due to capacity
- Patients already on steroids
- Patients with a history of steroid-related complications

#### METHODS AND PATIENT SELECTION:

Suitable patients will be identified from MDT

discussions. Consent to enter the trial will be obtained in the out-patient consultation prior to surgery. Confirmation of consent will occur after 48 hours of the first consultation. Full demographic data will be collected on all patients including age, BMI, gender, ASA grade, performance status and relevant co-morbidities. All patients will undergo CPEX testing prior to surgery and receive Level II/III care post-operatively.

Baseline investigations will be collected following full recruitment to the study. These will consist of VAS charts for pain, nausea & vomiting and fatigue. Baseline bloods including CRP, amylase and serum samples of TNF-alpha and IL-6 will be collected at the pre-operative assessment clinic. Demographic data, intraoperative and post-operative data will be collected prospectively using an existing database. The randomisation code will not be broken until after study completion and data analysis.

The treatment arm will receive 20mg of dexamethasone at induction; the non-treatment arm will receive an equivalent volume of placebo (normal saline). Post-operative bloods will be collected as per the collection timetable. Patients will be asked to complete VAS scores, QOR-40 and AT-4 scores assessing their nausea, pain, post-operative recovery, confusion, fatigue and delirium on days 1, 3, 5, and 10 post-operatively. Bloods will also be collected at these time-points. All patients will be part of an enhanced recovery protocolised pathway and will receive the same post-operative analgesia (intrathecal opiates via a spinal, wound infusion catheter and patient-controlled IV analgesia).

#### RANDOMISATION:

Patients will be allocated to a unique "kit number" decided by a randomisation spreadsheet, which will be developed and created by an independent third party (Welspring clinical services, Doncaster UK). Randomisation codes will only be broken once the study has been completed and following data analysis.

#### TIMELINE AND ETHICAL APPROVAL:

The study will be conducted from August 2020 to August 2021. Ethical approval is currently being applied for and the study will be conducted in accordance with the recommendations for Good Clinical Practice with support from the Leicestershire,

Northhamptonshire and Rutland Research Ethics Committee UK. Indemnity will be provided by the University Hospitals of Leicester.

#### STATISTICAL ANALYSIS AND POWER CALCULATION:

All data entry will be verified by the main researcher. Statistical analyses planned will  $\chi^2$  test and Fisher's exact probability test for categorical data. Student's t-test will be used for comparisons between time points and for comparisons between groups at a particular time point; equal variances will not be assumed. Analysis of variance (ANOVA) will be used to analyse the effects of steroids on the overall results, effect of time factor (time points) on the overall results in both groups and to determine if there is any interaction between both groups. In all cases, a value of  $P < 0.05$  will be taken to indicate statistical significance. Data will be presented as mean  $\pm$  SEM.

In order to demonstrate a 10% improvement in the primary outcome measures defined (given  $\alpha=0.05$ ) with a power of 80%; each group requires 63 patients. The HPB unit at the UHL undertakes 80 pancreaticoduodenectomies annually for suspected or proven periampullary cancer. It is anticipated that adequate recruitment will be achieved within two years. If recruitment exceeds this, further recruitment will ensue to improve the power of the study.

#### COSTS:

The funding applied for will be used to cover bench fees for ELISA assays to determine TNF-alpha and IL-6 levels.

Assay Kit Size	Single Kit	Price	Number of Kits required (triplicate tests at defined time points)
Treatment Arm	Number of Kits required (triplicate tests at defined time points)	Placebo Arm	Total Cost
IL-6	96 well Kit	£250	10 10 £5,000
TNF-alpha	96 Plate Kit	£350	10 10 £7,000
Total Cost			£12,000

#### STUDY PERSONNEL:

The lead investigators will be responsible for the clinical governance and trial design. Patient recruitment, data collection and bench work will be undertaken by a surgical trainee (ST5 or above) as part of his/her higher degree (MD). Salary will be provided by the UHL supporting the on-call

emergency rota but with no regular elective commitments. The successful applicant will be registered with the University of Leicester.

#### DISSEMINATION OF RESULTS:

This body of work will form the basis of higher degree and the study design, methodology, conduct and results will be incorporated into their written thesis. Results from the study will be presented at national and international pancreatic meetings and submitted for publication in suitable peer-reviewed medical journals with a target audience of pancreatic specialists. Any additional support received from will be openly acknowledged as a potential conflict of interest.

#### REFERENCES:

1. Malik SH et al. Effect Of Dexamethasone Versus Placebo For Improved Recovery In Patients Undergoing Anaesthetic Interventions For General Surgical Procedures. J Ayub Med Coll Abbottabad. 2019 Jul-Sep;31(3):422-426.
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does not increase the risk of postoperative wound infection: a propensity score-matched post hoc analysis of the ENIGMA-II trial (EnDEX). Br J Anaesth. 2017 Feb;118(2):190-199.

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13. Wente MN et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761-8.

## Timetable

<b>Name</b>	Ethics application
<b>Date</b>	Jan to June 2020

<b>Name</b>	Clinical Trial Start
<b>Date</b>	August 2020 to August 2022

<b>Name</b>	Data analysis and write-up
<b>Date</b>	August 2022 to Feb 2023

## Funding

<b>Name</b>	ELISA IL-6 (96 well kit) £250 per kit. 10 kits required in each arm of treatment and placebo.
<b>Amount</b>	5000.0

<b>Name</b>	ELISA IL-6 (96 well kit) £350 per kit. 10 kits required in each arm of treatment and placebo.
<b>Amount</b>	7000.0

## Details of ethical approval

In progress

## Institutional approval information

Department of HPB Surgery

GI Surgery Service

Cancer, Haematology, Urology, Gastroenterology, GI Surgery and Palliative Care (CHUGGS)

## Declaration

Confirm Declaration: Yes

Head of Department

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# View application from Jessica Hale

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Created: 30 Jan 2020, 3:58 p.m.

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## Institution Details

<b>Name</b>	University of Liverpool
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## Abstract

<b>Title of Study</b>	Stratification of pancreatic cancer according to microbiome directed tumorigenesis
<b>Abstract and methodological description</b>	Abstract: The progression model of cancer assumes that benign lesions develop into malignant cancer through a series of mutations. Intraductal papillary mucinous neoplasm

(IPMN) are assumed to be benign precursors of pancreatic cancer, partly because IPMN are often found alongside cancers. However, if an IPMN is still present it cannot have developed into the cancer and our hypothesis is that the IPMN has caused rather than developed into the malignancy. A possible mechanism for this is that oncogenic bacteria that have colonised biofilms in IPMN spread out down the duct. In this collaboration, bacterial populations in IPMN associated with cancer will be compared to bacteria within the cancer and in benign cystic lesions. A microbial signature associated with IPMN related cancer will be identified and clinical outcomes for patients with this signature will be contrasted with outcomes in patients where cancer development may be independent of the IPMN-bacteria-cancer pathway.

#### Background:

Intraductal papillary mucinous neoplasm (IPMN) are benign lesions that have a close association with Pancreatic Ductal Adenocarcinoma (PDAC). This is usually assumed to be because they represent precursors of cancer. IPMN found in the main duct of the pancreas are linked to the greatest risk of malignancy and NICE guidelines state that patients with such lesions should be offered surgery to remove the IPMN if that is feasible. IPMN in the branch ducts are more frequently identified and are less closely associated with development of PDAC. Patients with these lesions are offered surveillance to monitor possible progression rather than surgery. In Liverpool we host Europe's largest registry of families with genetic predisposition for pancreatic cancer. Individuals on this registry are offered secondary screening which involves imaging of the pancreas and IPMN are frequently identified. We have recently published on these findings, concluding that IPMN should be treated in the same way in high risk individuals as they are when encountered incidentally<sup>1</sup>. IPMN are found concomitant to PDAC in up to 10% of cancer cases, while confirming the association between IPMN and cancer this also shows that at least some IPMN lesions in cancer patients do not turn into pancreatic cancer. This suggests that there is either a link via a common susceptibility for the separate lesions (pancreatic cancer and IPMN) and that IPMN somehow causes pancreatic cancer or pancreatic cancer causes IPMN. In Familial Adenomatous Polyposis (FAP) individuals have a very

high frequency of polyp formation and hence an increased risk of colorectal cancer. Significantly, polyps found in FAP patients with colorectal cancer are colonized with carcinogenic bacteria found in their cancers and in cancers from patients with sporadic colorectal cancer. These bacterial populations are found in biofilms, which emanate within the polyp but extend out beyond them into the gut, suggesting that the polyps may be causing cancer to develop outside of the polyp and the link between the APC mutation and colorectal cancer may be due to polyps promoting cancer rather than cancer developing from the polyps<sup>2</sup>. By analogy bacteria within biofilms may be the link between IPMN and pancreatic cancer. IPMN certainly can have bacterial populations that are associated with cancer development<sup>3, 4</sup>. If the link between IPMN and pancreatic cancer is via bacteria in biofilms this would not of course mean that all cancers develop as a result of bacterial infiltration, but it could mean that this form of tumorigenesis is more likely where an IPMN is identified in a patient alongside a pancreatic cancer. Such cancers have been reported to be less aggressive than cancers where no separate IPMN is observed<sup>5</sup>. If pancreatic cancer concomitant with IPMN on average behaves differently to other pancreatic cancers and if this is because more of these cancers are the result of biofilm microbiota, then it is probable that cancers with IPMN biofilm associated bacterial populations will behave differently to treatment than cancers with other forms of microbiome. The microbiome is known to contribute to immunosuppression and hence resistance to immunotherapy<sup>6</sup>. It can also directly contribute to chemo resistance through bacterial inactivation of chemotherapeutic agents<sup>7</sup>. Therefore, the proposed project may provide insight into therapeutic response because of differential tumorigenesis (IPMN related compared to other) or because of the nature of the cancer microbiome itself (association of bacterial species and/or diversity and response).

Methodological description:

Aims and Objectives:

Hypotheses:

1. The microbial population in IPMN associated with cancer will be similar to the microbial populations in cancers associated with IPMN (IPMN-Cancer pattern)

and distinct from the microbial population in IPMN where no cancer develops and in cancers not associated with IPMN

2. Cancers with an IPMN-Cancer microbial pattern will have a different response to specific treatments than other cancers

#### Aims:

- (i) To identify an IPMN-Cancer microbial signature
- (ii) To establish associations between the IPMN-Cancer microbial signature with clinical outcomes and biomarkers (survival, progression, CA19-9 level, diabetes.)
- (iii) To establish associations between the IPMN-Cancer microbial signature in tissue and oral/intestinal microbial signatures

#### Objectives

1. Obtain aspirates of IPMN cyst fluid from patients under surveillance and from patients being screened for pancreatic cancer. Obtain saliva and faecal samples from these patients.
2. Obtain paraffin embedded fixed samples and frozen samples of resected main duct IPMN. Obtain saliva and faecal samples from these patients prior to surgery.
3. Obtain paraffin embedded fixed samples and frozen samples of pancreatic ductal adenocarcinoma from patients where no IPMN are identified. Obtain saliva and faecal samples from these patients prior to surgery.
4. Obtain paraffin embedded fixed samples and frozen samples of matched cancer and IPMN from patients with concomitant IPMN and pancreatic cancer. Obtain saliva and faecal samples from these patients prior to surgery.
5. Identification and quantification of bacterial genera in samples obtained as in objectives 1 to 4 by gene panel Next Generation Sequencing of bacterial DNA.
6. Carry out in-situ hybridisation of fixed samples to identify and localise particular microbial species.
7. Use of principal component analysis to identify discriminators amongst the bacterial populations between different sample types from the tumours (e.g. IPMN associated with cancer and their matched cancers against the rest, cancer associated with IPMN against cancer not associated with IPMN, IPMN from screened individuals against incidental IPMN from patients under surveillance etc.).

8. Identification of discriminating bacterial species (from objective 7) in fixed samples.
9. Use of data from objectives 7 and 8 to identify a possible IPMN-Cancer microbial signature.
10. Classification of patients according to presence or absence of the IPMN-Cancer microbial signature in cancers or IPMN.
11. Use of principal component analysis to identify discriminators amongst the bacterial populations in stool and saliva samples between patients defined as in objective 10.
12. Association analysis of patient classification (according to microbial signature) with clinical outcomes and biomarkers.

#### Work Plan:

Methods for microbiota analysis have been developed and refined by the Bruce group for two decades. From each individual enrolled in this study, samples (saliva, faeces and where relevant IPMN cyst fluid) will be biobanked. SOPs for the analysis of the microbiota in many sample types e.g. faeces have been developed and are in constant use. Funding though is requested to derive a robust SOP for IPMN cyst fluid analysis. By applying these protocols, we will gain information of immediate clinical relevance e.g. in terms of the variation in microbiota composition in IPMN as sampled at different locations within the same individual or wider. Clinical samples will also be stored in the Study Biobank as paraffin embedded fixed samples and frozen samples. During this sample collection and process validation phase, it is likely the rate of accumulation of clinical material will vary with certain tissue/ specimen types more common. For these more common tissues/ specimen types, we will look to obtain material extending the initial remit from an exclusively cross-sectional to include longitudinal sets of data. Microbiota data – primarily bacterial genera identification (high through put sequencing) and bacterial load estimation (quantitative PCR) – will be combined with clinical metadata. By applying statistical tools e.g. principal component analysis, discriminators amongst the bacterial communities present on tumours (e.g. IPMN associated with cancer and their matched cancers against the rest, cancer associated with IPMN against cancer not associated with IPMN, IPMN from screened individuals against incidental IPMN from patients under surveillance etc.) will emerge. This may identify a possible IPMN-



Cancer microbial signature which has in itself alone exciting applications e.g. as biomarkers. This application represents an opportunity for the Clatterbridge Cancer Centre, the University of Liverpool and King's College London to forge a new collaboration. The samples will be collected and stored using the established expertise of the Liverpool GCPLab facility. Microbiome analysis will be carried out in King's College London by the established leaders in this field. Clinical data will be recorded and linked to laboratory data at the CCC and statistical analysis of associations will be carried out by the lead cancer statistician of the LCTC.

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randomised, double-blind, placebo-controlled BLESS trial. Lancet Respir Med 2015;3:e15.
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## Timetable

<b>Name</b>	Ethical approval from local committee at Clatterbridge Cancer Centre
<b>Date</b>	February 2020

<b>Name</b>	Biobanking of samples to begin in February 2020 and continue throughout the year as samples become available. Aim to collect 100 samples within a 12 month period.
<b>Date</b>	March 2020- February 2021

<b>Name</b>	Obtain microbiota data (bacterial genera identification using high throughput sequencing) and bacterial load estimation (quantitative PCR)
<b>Date</b>	March 2020- February 2021

<b>Name</b>	Statistical analysis (combine microbiota data with clinical metadata)
<b>Date</b>	March 2021

<b>Name</b>	Preparation of manuscript for publication
<b>Date</b>	April 2021

## Funding

<b>Name</b>	Sample collection (staff)
<b>Amount</b>	355.0

<b>Name</b>	Lab analysis (Liverpool) -staff
<b>Amount</b>	946.0

<b>Name</b>	Lab analysis (kings)- staff
<b>Amount</b>	2365.0

<b>Name</b>	Next-generation sequencing (kings)
<b>Amount</b>	4950.0

<b>Name</b>	Sample collection/storage
<b>Amount</b>	60.0

<b>Name</b>	Immunohistochemistry analysis
<b>Amount</b>	175.0

## Details of ethical approval

Biases caused by sample collection and processing means that this study is unsuitable for retrospectively collected samples and all samples will therefore be collected prospectively with full informed consent. Ethical approval for this study will be obtained from the relevant committee at Clatterbridge Cancer Centre.

## Institutional approval information

The study hypotheses were developed during discussions between Professors Palmer (Director of the Liverpool ECMC), Greenhalf (ECMC translational scientist), Bruce (Senior Lecturer, Kings College) and Fine (Senior Lecturer Southampton). Dr Jessica Hale carried out the necessary literature search for the application and will lead the laboratory work in Liverpool as part of her CCC-funded PhD clinical fellowship. Professor Halloran is a consultant surgeon and clinical lead for Europe's largest screening programme for pancreatic cancer (EUROPAC), he is therefore able to help in identification of patients and in obtaining samples. Dr Richard Jackson is the lead cancer statistician in the LCTC and as such has the expertise necessary to properly control for clinical variants in the complex analysis necessary for this study. Ms Charlotte Rawcliffe and Ms. Sara Martin are key members of the ECMC operational team who have co-ordinated the collaboration as it has developed to date and will continue to support the project during its progression.

## Declaration

Confirm Declaration: Yes

Head of Department

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