## ORAL PRESENTATIONS 5A
## FUTURE PROJECTS (2)

### O114 A MULTIMODAL INTERVENTION (NUTRITION, EXERCISE AND ANTI-INFLAMMATORIES) FOR THE PREVENTION OF MYOSTEATOSIS IN PATIENTS WITH INOPERABLE PANCREATIC CANCER

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**Introduction:** Myosteatosis is the infiltration of lipid into the inter- and intramyocellular compartment and is quantified by the attenuation of skeletal muscle Hounsfield units (HU) on CT imaging. Myosteatosis has an incidence of approximately 70% in patients with inoperable pancreatic cancer and evidence suggests this is associated with a significant reduction in survival.

**Study Design:** This study is a single-centre, pilot interventional randomised controlled trial comparing a multimodal intervention (nutritional supplementation, anti-inflammatories and physical exercise) combined with standard pancreatic cancer care versus standard pancreatic cancer care alone. The primary aim of this study is to evaluate the effect of multimodal therapy on the incidence and severity of myosteatosis in patients with inoperable pancreatic cancer during palliative chemotherapy. Pilot Plan This pilot study will recruit 40 patients due to undergo palliative chemotherapy for inoperable pancreatic cancer; 20 to the intervention versus 20 to the control. The data from this pilot study will be used to inform compliance and attrition rates which will be used in sample size calculations for a larger study. We anticipate that recruitment of 40 patients will take approximately 18 months. Forward Plan This pilot study is planned prior to seeking funding for a larger scale interventional study to examine the role of this intervention in patients with inoperable pancreatic cancer. If successful, this would have a huge clinical impact and relevance to a large patient population, providing evidence for a simple, effective, clinically implementable treatment for the unmet burden of myosteatosis in palliative disease.

**Take-home message:**
Myosteatosis is the infiltration of fat into the inter- and intramyocellular compartments and is associated with a significant reduction in patient survival in pancreatic cancer. This planned pilot interventional study aims to study the impact of a multimodal intervention (exercise, nutrition and anti-inflammatories) upon the incidence and severity of myosteatosis in patients with inoperable pancreatic cancer and, perhaps, as a secondary outcome, to improve quality of life and survival in patients with inoperable pancreatic cancer.

### O115 VALIDATION OF TOTAL PELVIC FLOOR UTLRASOUND IN PELVIC DEFAECATORY DYSFUNCTION

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**Introduction:** Total pelvic floor ultrasound (transperineal, transvaginal) may provide an alternative assessment tool to defaecation proctography for pelvic floor defaecatory dysfunction.

**Study Design**: A prospective, observational study of 20 asymptomatic female volunteers and 170 women presenting with defaecatory dysfunction. (Powered to a parous rectocoele incidence of 60% and 20% in nulliparous women for an 80% power and a 95% significance level). Asymptomatic women will undergo clinical examination, total pelvic floor ultrasound and defaecation MRI. The MRI will delineate anatomical features which will be correlated with ultrasonic appearances. Symptomatic women undergo clinical examination, symptom severity scoring, pelvic floor ultrasound and defaecation proctography. Inter and intra - rater repeatability of ultrasound interpretation and measurement will be assessed. Correlation of pelvic floor ultrasound with clinical examination and symptom severity scores and accuracy will be reviewed. Pilot Data A retrospective study of 393 undergoing total pelvic floor ultrasound and proctography established an accuracy of ultrasound (rectocoele positive predictive value 92%, negative predictive value 25%). All rectocoeles causing barium trapping on proctogram were detected using ultrasound. Those visualised on both transperineal and transvaginal ultrasound were significantly more likely to trap barium ($p=0.03$) and require surgery ($p=0.05$) than if visible on one view. Forward Plan If total floor ultrasound is accurate and repeatable, women with defaecatory dysfunction will no longer undergo proctography but rather, simply undergo total pelvic floor ultrasound in clinic. Total pelvic floor ultrasound will be used to plan treatment and select those who will benefit from further assessment of defaecatory dynamics with proctography. MRI - Magnetic Resonance Imaging

**Take-home message:**
This will be the largest prospective study to compare pelvic floor ultrasound with defaecation proctography, the first to correlate ultrasound with symptoms and the first to examine total pelvic floor ultrasound in asymptomatic volunteers. If total floor ultrasound is accurate and repeatable, total pelvic floor ultrasound may replace defaecatory proctography as the initial investigation of choice for women with pelvic floor defaecatory dysfunction.

## O116 EVALUATION OF A NOVEL MITOCHONDRIA-TARGETED ANTI-OXIDANT THERAPY FOR ISCHAEMIC REPERFUSION INJURY IN A MODEL OF KIDNEY TRANSPLANTATION

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**Introduction:** IRI is inevitable in kidney transplantation and leads to delayed graft function, resulting in significant morbidity and increased healthcare costs. As mitochondria play a central role in the generation of ROS during IRI, we examined the efficacy of the novel mitochondria-targeted antioxidant MitoQ in amelioration of renal IRI using pig and human kidneys.

**Study Design**: Under UK animal legislation, kidneys were retrieved from anaesthetised pigs after 10 min of warm ischaemia, flushed with cold HOC ±MitoQ and stored in ice for 10h. Pig kidneys were reperfused ex-vivo with oxygenated autologous whole blood for 6h to assess renal function and injury. Human kidneys retrieved for transplantation but subsequently declined were similarly flushed and stored with cold HOC ±MitoQ and reperfused ex-vivo with ABO group matched blood. Pilot data In the porcine model, renal blood flow and urine output were significantly higher in the 50μM group compared to the controls (115±15 vs. 33±7 mL/min/100g; P=0.001, 678±208 vs. 309±112 mL/100g; P=0.007 respectively). Preliminary data using declined human kidneys also demonstrated a trend towards improved function after MitoQ treatment. Forward plan Preliminary data suggest that treating kidneys with MitoQ during the cold preservation period may ameliorate the detrimental effects of IRI. The next stage will be to test the safety and efficacy of MitoQ using a larger numbers of pig and human kidneys and in a pre-clinical transplant model. MitoQ has the potential to increase the use of marginal kidneys and to improve graft and patient outcomes. IRI Ischaemia Reperfusion Injury ROS reactive oxygen species HOC Hyperosmolar citrate preservation solution

**Take-home message:**

Preliminary data suggest that treating kidneys with MitoQ during the cold preservation period may ameliorate the detrimental effects of IRI. MitoQ has the potential to increase the use of marginal kidneys and to improve graft and patient outcomes after kidney transplantation.

## O117 MICRORNA EXPRESSION IN THE RECTAL MUCOSA: RESPONSE TO BARIATRIC SURGERY AND IMPLICATIONS FOR COLORECTAL CANCER RISK. (ISRCTN95459522)

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**Introduction**: Obesity is a well-established risk factor for colorectal cancer (CRC), but the impact of weight loss on CRC risk is less clear. Epidemiological and mucosal biomarker studies suggest that gastric bypass may have an unexpected adverse impact on CRC risk. MicroRNAs regulate gene transcription and show deranged patterns of expression in CRC. Our aim is to assess alterations in microRNA expression in response to bariatric surgery and to investigate the links to CRC-relevant molecular pathways.

**Study design**: 38 patients listed for bariatric surgery and 20 non-obese control volunteers were included (REC approval-13/NE/0204). Extensive phenotype data and biological samples were collected, before and at 6 months post-operatively. We assessed whole miRNA genome profile of rectal biopsies using real-time quantitative polymerase chain reaction (qPCR). Bioinformatics and in silico target prediction tools were used to identify potentially relevant molecular pathways. Pilot data: Expression of 8 miRNAs was significantly and consistently altered from baseline to post-operatively. Interestingly, miRNA-143, identified as a tumour suppressor in CRC, shows an over twofold reduction in expression after bariatric surgery, suggestive of an increase in CRC risk. Forward plan: Validated miRNAs will be used to identify relevant gene targets for subsequent gene expression analysis. Findings will be correlated with changes in established mucosal biomarkers of CRC risk. This study will help increase our understanding of the mechanistic pathways involved in obesity-related CRC risk and the potential impact of bariatric surgery. Findings from this study may be the basis for development of novel biomarkers for surveillance of this patient population.

**Take-home message:**

This study aims to investigate obesity-related CRC risk and the impact of bariatric surgery. Current investigation is being guided by preliminary data showing changes in expression of microRNAs involved in the regulation of CRC-relevant genetic pathways.

## O118 A PROSPECTIVE RANDOMOSED STUDY IN DIRECT VISUAL TRAINING IN LAPAROSCOPIC SIMULATION.

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**Introduction:** Laparoscopic simulation training is an important tool in the era of EWTD and reduced theatre exposure. Stereopsis is a contributing factor to the steep laparoscopic learning curve and mental workload. Direct visual training (DVT) consisting of performing laparoscopic tasks under direct vision

rather than by visualising a laparoscopic image on a screen. This study aims to determine the effects of DVT on laparoscopic skill acquisition and mental workload.
**Study design:** Twenty medical students with no previous laparoscopic exposure will be randomised into 2 training regimens. A control group will undergo standard laparoscopic simulator training (LST). The experimental group will undergo initial DVT followed by LST. Participants will be tested on 3 laparoscopic tasks (ring transfer, precision cutting and knot tying) and scored by 2 blinded assessors. Serial mental workload data will be collected using a validated scoring system (NASA-Task Load Index). The main outcome measure was % reduction in time to complete a laparoscopic task. PILOT DATA Initial data from this study demonstrated that DVT led to greater improvement in task completion compared to the LST group (% reduction in time DVT v LST: ring transfer 77% vs 38%; precision cutting 42% vs 13%). Participant's perception of difficulty and mental workload were reduced following both modes of training. FORWARD PLAN This study will determine the effects of DVT on laparoscopic training. By optimising laparoscopic training outside of the operating theatre, it will assist surgical trainees in utilising their time better in theatre for the benefit of future patient care.
**Take-home message:**
By optimising laparoscopic training outside of the operating theatre, it will assist surgical trainees in utilising their time better in theatre for the benefit of future patient care.

## O119 IMPLEMENTATION SCIENCE: A BAYESIAN PREDICTION TOOL FOR ACUTE TRAUMATIC COAGULOPATHY

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**Introduction**: Globally, two million trauma patients die annually from exsanguinating haemorrhage. Acute traumatic coagulopathy (ATC) is a consequence of major trauma occurring within minutes of injury and presents in 25% of cases. ATC is associated with a 5-fold increase in mortality, significantly greater transfusion requirements, organ injury, septic complications and critical care stay.
**Study Design**: A Bayesian Network (BN) decision support tool that predicts the presence of traumatic coagulopathy has been constructed. BNs are powerful probabilistic mathematical models that fuse published evidence with expert knowledge and are validated with information accrued from clinical databases. Our ATC model requires basic clinical information available within the first 15 minutes of patient reception. Pilot Data: Internal and external validation on 900 trauma patients revealed excellent predictive power (Area Under the Receiver-Operator Curve of 0.93; specificity of 82% at sensitivity threshold of 90%) with good accuracy (Brier score 0.06). It adjusts for missing data and has an interface that helps to explain the rationale for its predictions to the end-user. Having firmly established Proof of Concept we now wish to assess whether the surgical care of major trauma patients can be improved through use of this decision support tool. Forward Plan: Implementation science identifies and addresses barriers that impede successful implementation to promote integration of research findings and evidence into healthcare policy and practice. A feasibility randomised clinical trial will demonstrate that the ATC BN forms the basis of a clinical decision tool where predictive accuracy is only the first step.
**Take-home message:**
Early and accurate prediction of the risk of ATC heavily influences surgical strategy in major trauma patient care and leads to improved patient outcomes. Successful uptake of an optimised ATC BN has the potential to improve surgical decision-making, resource utilisation and patient care in complex poly-trauma patients.

## O120 INVESTIGATING GENOTYPIC CHANGES IN CHRONIC WOUND FIBROBLASTS

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**Introduction:** Chronic wounds are a major cause of disability worldwide; resulting in increasing inpatient numbers and post-operative compliactions. Healing-rate decreases with age due to impaired differentiation of fibroblasts into myofibroblasts, contractile cells responsible for wound closure. Age-related fibroblast dysfunction is associated with impaired hyaluronan synthase-2 (HAS2) and epidermal-growth-factor-receptor (EGFR) function, as well as over-expression of microRNA-7 (miR-7) which antagonises EGFR. This interferes with myofibroblast formation thus impairs wound closure. We aim to determine whether similar mechanisms operate to impair wound healing responses of chronic wound fibroblasts (CWF).
**Method:** Four patient matched samples of CWF and normal fibroblasts were cultured in HAMS-F12/DMEM containing foetal-bovine-serum. Half of the cells were treated with Transforming-Growth-Factor (TGF)-β1, to induce differentiation; half remained as negative controls. mRNA was extracted, followed by reverse transcription and QPCR to determine levels of expression of the following genes: a-SMA (myofibroblast marker), EGFR, CD44, HAS2 and miR-7 in the chronic versus normal fibroblasts.
**Result:** a-SMA mRNA and protein expression decreased in CWF but increased in both chronic and normal fibroblasts with TGF-β treatment. EGFR expression decreased in CWF, TGF-β treatment increased levels of EGFR in both samples. CD44 and HAS2 showed no significant change. miR-7 expression increased in TGF-β treated CWF.
**Conclusion:** There are significant phenotypic similarities between CWF and aged fibroblasts. Greater

focus on the mechanism involved in miR-7 over-expression in CWF and whether silencing this gene improves function could be an exciting avenue to explore in developing new therapies to increase wound healing in the acute and chronic setting.

**Take-home message:**

Chronic wounds are a major cause of morbidity and disability worldwide, increasing inpatient stay and post-operative complications in the acute and chronic setting. A greater understanding of the changes in fibroblasts on a cellular level could provide exciting, more effective avenues for therapy to increase healing rates and improve patient outcomes and quality of life.

## O121 MODULATING THE P53/MDM2 AXIS TO ENHANCE OUTCOMES OF RADIOTHERAPY FOR HEAD & NECK CANCER: TUMOUR AND NORMAL TISSUE STUDIES IN VITRO AND IN VIVO

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**Introduction**: Squamous cell carcinomas of the head and neck (HNSCC) exhibit variable responses to radiotherapy (RT). Despite advances in treatments, five year survival rates for HPV- disease remain at 60%, and acute and late toxicities are severe.

**Study Design**: Using primary HNSCC cell lines and subcutaneous xenografts we will investigate the radiosensitising potential of p53 activation by testing Nutlin compounds (RG7112 / RG7388) in models of p53 mutant, HPV- SCCHN. Radiosenstivity will be measured by clonogenic survival and tumour growth delay and mechanisms investigated using established assays of cell death signalling and effector pathways. For radiation toxicity studies Mdm2 ΔP1/ΔP1, Mdm2 P2/P2 and wild type mice will be exposed to whole body irradiation (2Gy-10Gy) and normal tissue effects measured by immunohistochemistry. Pilot Data: The most common genetic lesion in HNSCC is TP53 gene mutation. The p53 tumour suppressor protein is a critical coordinator of radiation responses and we have demonstrated that Nutlin-3, an antagonist of MDM2 the major negative regulator of p53, significantly increases radiation sensitivity. MDM2 antaogonists have been shown to exert protective effects on p53 wt human fibroblasts treated with cytotoxic agents. We propose that MDM2 inhibitors might have radioprotective effects on p53 wt normal tissues while enhancing the radiosensitivity of p53 mutant HNSCC. Forward Plan: To generate novel and clinically important data describing the effects of enhanced p53 expression on normal tissue radiation effects, and to provide pre-clinical proof of principle for MDM2 antagonism as a tumour specific radiosensitising agent for p53 mutant cancers including HPV- HNSCC.

**Take-home message:**

To generate novel and clinically important data describing the effects of enhanced p53 expression on normal tissue radiation effects, and to provide pre-clinical proof of principle for MDM2 antagonism as a tumour specific radiosensitising agent for p53 mutant cancers including HPV- HNSCC.

## O122 A PROSPECTIVE, MULTICENTRE STUDY ON THE USE OF EPIDERMAL GRAFT TO OPTIMISE OUTPATIENT WOUND MANAGEMENT

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**Introduction:** Current wound management with the use of split thickness skingrafts often requires hospital admission, a period of immobility, attentive donor site wound care and pain management. This study evaluates the feasibility of using a novel epidermal graft harvesting device (CelluTome) which allows pain-free epidermal skin grafting in the outpatient clinic setting.

**Method:** A prospective series of 35 patients was performed in 2 centres, involving 10 acute and 25 chronic wounds. All patients were subjected to epidermal grafting in the outpatient specialist clinic, without the use of anaesthesia, and allowed to return home after the procedure.

**Result:** Completely healed wounds were noted in 22 patients (62.9%).The overall mean time for 50% and 100% reduction in wound size was 3.31±2.33 weeks and 5.91±3.48 weeks respectively. There was no significant difference in healing times between the acute and chronic wounds (50% reduction in wound size; acute 2.20±0.91 weeks versus chronic 3.73±2.63 weeks, p=0.171. 100% reduction in wound size; acute 4.80±1.61 weeks versus chronic 6.83±4.47 weeks, p=0.183). The mean time for donor site healing was 5.49±1.48 days. The mean pain score during graft harvest was 1.42±0.95 and the donor site Vancouver Scar Scale was 0 for all cases at 6 weeks. CONCLUSION This device offers skin harvesting in the outpatient setting with minimal or no pain and a scarfree donor site. It has the potential to save NHS resources by eliminating the need for theatre space and a hospital bed, while at the same time benefiting patient care.

**Take-home message:**

Epidermal Grafting allows for pain free autologous grafting in the outpatient setting and can be a useful tool in the management of acute and chronic wounds.

## O123 INVESTIGATION OF THE MOLECULAR EFFECTS OF COOLING HUMAN BURNS

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**Introduction:** Cooling is a mainstay of burn-management. Clinical series show cooled burns need fewer skin grafts, and animal models demonstrate reduced burn progression. However, it is not understood how cooling mediates these benefits.
**Study design**: We designed an ethically approved human thermal injury model using abdominal skin normally discarded during breast reconstruction surgery, and apparatus to create standardised burns and administer standardised cooling after anaesthesia (Regional Ethics Committee Reference 13/SC/0518). Cooling is administered to one set of burns and control areas, and the burns and corresponding unburned controls are harvested at 1-3 hours. Half of each specimen is formalin-fixed for histopathology, and half snap-frozen. Pilot data We recruited 25 patients. Calibration established that 7.5 seconds contact with the burn-creation device produced consistent mid-depth injuries clinically, and microscopically, and this duration was used henceforth. Paired burn comparisons at 1 and 3 hours showed significantly deeper microvascular occlusion in both cooled ($p=0.042$) and non-cooled burns ($p=0.015$) at 3 hours. Cooling significantly reduced burn depth at 1 hour ($p=0.0048$) and 3 hours ($p=0.0024$). RNA from paired frozen specimens was submitted for sequencing. Forward plan We have demonstrated the relationship between microvascular damage and contact-time, its biological progression with time, and its response to cooling, mirroring the clinical appearance of the burns. The RNA sequencing, and subsequent immunohistochemistry and proteomic validation will give unprecedented insight into the effector-mechanisms of cooling. Molecular targets identified could be used in pharmacological burn-management when actual cooling is not safe- very large burns at risk from hypothermia- or possible- mass-casualties and battlefield injuries.
**Take-home message:**
Microvascular damage is a very early, progressive feature of thermal injuries. Cooling mediates its beneficial effects upon burns, at least in part, by protecting the microvasculature from progressive occlusion.

## O124 A RANDOMISED CONTROLLED TRIAL TO ASSESS THE IMPACT OF PATIENT SPECIFIC MENTAL REHEARSAL ON SURGICAL PERFORMANCE

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**Introduction**: Empirical evidence demonstrates that rehearsing a task mentally enhances its subsequent performance. Several studies indicate these techniques to be applicable in surgery. This study aims to compare a patient specific mental rehearsal process to a generic one.
**Study design**: Through semi-structured interviews, experts will be asked to describe how they perform laparoscopic cholecystectomy, focusing on visual and kinaesthetic cues. According to the transcripts, a Structured Mental Rehearsal (SMR) checklist will be created. Sample size calculations show that 16 participants are required (Competency assessment tool – CAT - 3 versus 2). They will be randomised to two groups. All will perform 6 virtual laparoscopic cholecystectomies (VLC). Anatomy will vary for each procedure. Group 1 will be using the SMR checklist and an anatomy specific 3D model, prior to each procedure. Group 2 will be using the checklist only. The primary outcome of study will be surgical performance, which will be assessed using CAT for laparoscopic cholecystectomy. Pilot data: To assess feasibility, a smaller scale pilot study was conducted. 3D models were compared to didactic videos. Trainees who performed SMR using a 3D model performed significantly better (number of movements - 553 vs. 1391.5, $p=0.005$, total path length of instrument tip 1540.24 vs. 2837 $p=0.007$ and time 667s, vs. 1283s, $p=0.003$). Forward plan: This pilot study is expected to highlight the importance of patient-specific SMR as a tool of augmenting quality of surgery. As a secondary outcome, it will establish a scientifically tested methodology for the creation of SMR checklists in surgery.
**Take-home message:**
This pilot study is expected to highlight the importance of patient-specific SMR as a tool of augmenting quality of surgery.