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View application from Rupaly Pande

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Abstract

Title of Study	PARANOIA: The Pancreatic Anastomosis Audit
Abstract and methodological description	<p>Abstract</p> <p>Aim: To develop an international registry for the collection, investigation and assessment of factors related to post-operative pancreatic fistula development. The registry will permit analysis of risk factors, provide users risk adjusted CUSUM outcomes and will be used to implement and assess interventions aimed to reduce POPF.</p> <p>Introduction</p> <p>Postoperative pancreatic fistula (POPF) is the single most important complication following pancreatoduodenectomy (PD), impacting hospital stay and cost, complications and post-operative mortality. Furthermore, POPF may delay, if not all together deny patients the opportunity to receive adjuvant chemotherapy. Clinically relevant POPF (CR-POPF) affects around 15% of patients and is associated with a large financial burden where its occurrence doubles healthcare costs.</p> <p>There are many flaws in the current understanding of POPF, how surgeons review their outcomes and of trials to reduce POPF. Firstly POPF risk varies widely from patient-to-patient but adjustment of risk is not undertaken routinely, but is possible using published risk scores. Adjusted outcomes would permit surgeons to critically evaluate their practice. A meta-analysis by this group further shows that the vast majority of RCT's testing an intervention to reduce POPF are underpowered. This is more of a problem with the move to CR-POPF which has reduced the incident rate of POPF. Thus, facilitating multicentre studies where recruitment could be quick and with a flexible design means that a registry would be an excellent way to overcome existing barriers to research.</p> <p>Methods: Phase 1) Evidence and Awareness: To conduct systematic reviews and meta-analyses of the literature to inform the core dataset and future</p>

studies. To test the registry on a UK cohort and create awareness and use of dataset across five specialist sites in mid-2021.

1) Published studies

a) A Systematic Review and Meta-Analysis of Factors Associated with postoperative Pancreatic Fistula (POPF) following Pancreatoduodenectomy

2) Studies under submission

a) External validation of post-operative pancreatic fistula prediction scores in pancreatoduodenectomy: a systematic review and meta-analysis

b) A Systematic Review and Meta-Analysis of Interventions to Reduce Postoperative Pancreatic Fistula after Pancreatoduodenectomy?

c) Can trainees safely perform pancreatoduodenectomy ? A systematic review, meta-analysis and risk-adjusted analysis of post-operative pancreatic fistula

d) Systematic review of the impact of perioperative factors on postoperative pancreatic fistula following pancreaticoduodenectomy

3) Ongoing study

a) Systematic review to assess the power of the evidence behind randomised controlled trials for interventions of anastomotic leaks.

Phase 2) Establishing the registry. A twelve-month international multicentre prospective audit will be performed starting in 2021. Patients undergoing pancreaticoduodenectomy over 12 months with a 90-day follow up period. The results will be analysed against set global standards found within the literature. Audit standards assessed:

- expected CR-POPF rate 15%

This will be followed by several parallel studies, initiated by users who will be able to use the platform conduct their research. Such studies would include assessment of novel risk factors for POPF, comparison of trainee and trainer outcomes, comparison of surgical techniques and POPF and to obtain preliminary data to support a clinical trial.

Phase 3) Creating a legacy: The development of an international registry which can be freely available to users will help towards a much greater understanding of POPF. Providing surgeons with their risk adjusted outcomes will hopefully

ensure the continued use of the registry in the long term ensuring its continued success.

Conclusion:

This is an innovative next step in our understanding of POPF in an era where there is a greater scrutiny of outcomes from both professional and public spectators. The platform provides both risk adjusted CUSUMs and a registry which allow trials to be conducted avoiding the common methodological pitfalls and thus generating more representative evidence-base for practice.

Importance and potential of the work

Despite advances in technology and healthcare 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 evaluating risk and studies are largely negative i.e. fail to demonstrate benefit of the tested intervention.

The approach of 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 initiated through a similar local network eg. OGAA (Oesophago-Gastric Anastomosis Audit, multicentre prospective audit to analyse current techniques of oesophagogastric anastomosis to determine the effect on the anastomotic leak rate.) and EAGLE (EAGLE: An international, cluster randomised-sequence study of a 'Safe-anastomosis' Quality Improvement Intervention to reduce anastomotic leak following right colectomy and ileocaecal resection) have successfully demonstrated, through publications in high impact factor journals, the ability to capture data on thousands of patients overcoming geographic and methodological flaws associated with more traditional studies.

Thus, establishing a platform for the routine audit of POPF and the potential for initiating large scale studies is both highly attractive and achievable. This method can determine the accuracy of established risk scores and factors measured across the world in a short period which limits confounding from changes in practice over time or surgical technique due to the increased power that comes with large patient volume studies. Furthermore, an individual's risk

of POPF varies widely and thus providing users with their own risk adjusted CUSUM plots takes into account this variation and provides users 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 registry 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 which will also answer relevant research questions.

1. Determine which factors to include with the database through systematic review and meta-analysis – COMPLETED NOVEMBER 2020
2. Develop the database for the routine collection of variables using the REDCap secure web application in conjunction with the BiSTC – NEAR COMPLETION
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).

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

Several systematic reviews and meta-analyses have informed the dataset and primary objectives:

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. This meta-analysis sought to assess the safety of trainees performing PD through critical evaluation of POPF rates between trainees and established surgeons by a combination of meta-analysis of data and a risk adjusted analysis using published risk scores PD, when performed by trainees, is associated with acceptable outcomes. There is evidence of case selection among patients undergoing surgery by trainees; hence, risk adjustment provides a critical tool for the objective evaluation of 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 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. 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 (June 2021-2022) 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.

A 2-month pilot of 5 centres (UK/international), will be undertaken to finalise the detailed online case report forms prior to the global audit.

Study Population

Inclusion Criteria

- Pancreatoduodenectomy

Exclusion criteria

- Age <18y

Patient identification

- MDT
- Coordination with lead surgeon and HPB Specialist nursing services
- Review of theatre lists

Centre Eligibility

Any centre routinely performing pancreatic resections. No restriction on global location or number of surgeons involved.

Data Completion and Organisation

Data input will be via a dedicated encrypted server through the Research Electronic Data Capture (REDCap) web application hosted by BiSTC. No patient identifiable information will be inputted. Locally held records containing corresponding REDCap ID numbers and local patient identifiers must be stored securely.

Data will be entered into case report forms (CRFs) 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. Data will be stored securely on encrypted and certified servers for a minimum of 5 years.

Research environment and people

PARANOIA is an international multicentre study run in association with many supporting groups, namely Birmingham Surgical Trials Consortium (BiSTC), Royal College of Surgeons of England, GBIHPBA, AUGIS.

Rupaly Pande is a research registrar at the HPB unit in Birmingham conducting her PhD on "Development of a novel platform for understanding POPF through overcoming barriers to research". She is on the steering committee for RICOCHET (Receipt of Curative resection Or palliative Care for HEpato-pancreato-biliary Tumours) and IMPROVEPanc and has published on Fast Track and pancreatic surgery.

BiSTC boast a portfolio of over 35 trials currently ongoing and successes such as ROCSS (Reinforcement of Closure of Stoma Site. A randomised controlled

trial of reinforcement of closure of stoma site using a biological mesh). Chaired by Professor Pinkney, who has extensive experience in large global collaborative studies and was also a founding member of the West Midlands Research Collaborative, and responsible for three multicentre RCTs, five observational cohort studies and 43 publications to date.

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

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.

Collaborators: The PARANOIA Study Group is fortunate to have a wealth of highly motivated experts within the field with several other globally recognised names enthusiastic to partake. Such a diversity experience and experts invested in propelling research into pancreatic cancer will help guide and ensure PARANOIA becomes a platform for greater success.

Prof Kevin CP Conlon -Ireland, Secretary General IHPBA,

Professor Ajith Siriwardena- Manchester - congress President for E-AHPBA 2015

Professor Bobby Tingstedt, Chairman for the National Guidelines Group for Pancreatic Cancer Sweden

Nicola de Liguori Carino- Manchester

Professor Sohei Satoi- Japan,

Stefan Statner - Austria,

Professor Darius Mirza & Robert Sutcliffe - Birmingham

Francesco Giovinazzo- Italy,

James Skipworth- Bristol

Ali Arshad - Southampton,

Sanjay Pandanaboyana - Newcastle

Benjamin Loveday - Australia

Todd Hore- New Zealand

Timetable

Name	Series of Webinars to discuss results of systematic reviews and audit goals; Commence Registration of Interest.
Date	February 2021
Name	Completion of systematic review and meta-analyses
Date	March 2021
Name	Feasibility test at 5 sites
Date	March – April 2021
Name	12 month International audit of POPF
Date	June 2021

Funding

Name	Data manager (Band 6) at 0.25% FEC (no overheads), for 12 months
Amount	6500.0
Name	Statistical software costs
Amount	3000.0
Name	Contribution to statistician costs
Amount	500.0

Name	A key factor in the delivery of this project is our ability to utilise significant support from the new unit for prospective non-randomised surgical studies at the University of Birmingham (chaired by
Amount	10000.0

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: Yes

Head of Department

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