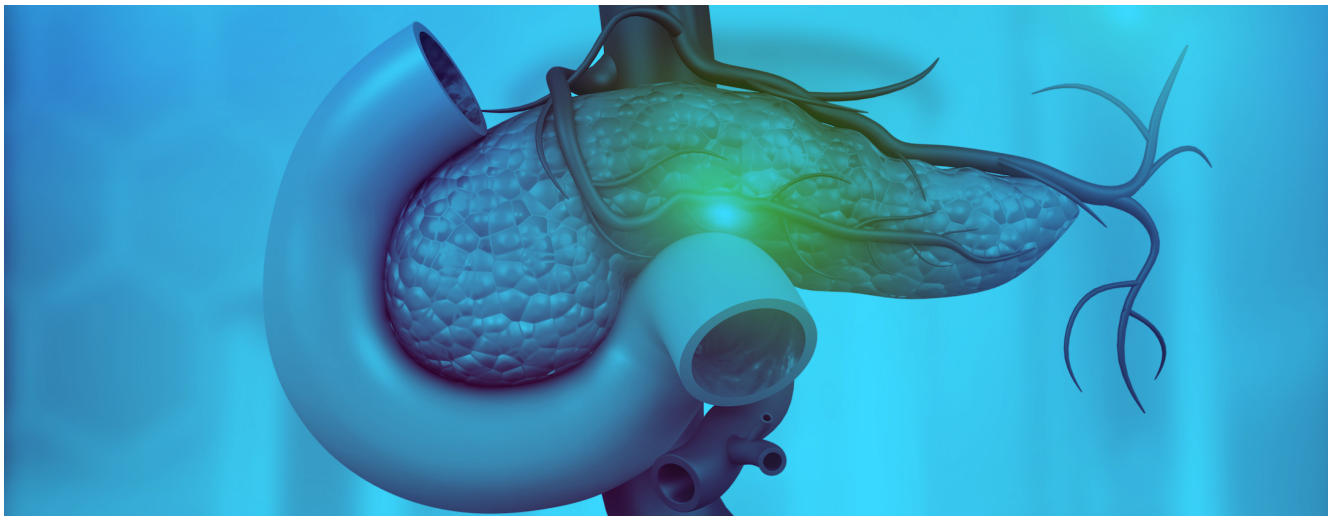
Study Protocol



International Snapshot Study on the Outcomes of Pancreatic Surgery – PancreasGroup.org

The PancreasGroup.org Collaborative[1,2,3]

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Protocol version

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To be approved by the Chief Investigators and all Members of the Scientific Committee (see below).

PancreasGroup.org, London, UK and Boston, USA

Trial registration: ClinicalTrials.gov - pending. ISRCTN – pending.

Roles and responsibilities:

The **headquarters** acting as the coordinating centre is located at the Royal Free Hospital in London, UK run by Dr. Dimitri Aristotle Raptis, Prof. Giuseppe Kito Fusai and the Management Committee.

The **Chief Investigators** of PancreasGroup.org are Prof. Giuseppe Kito Fusai from the Royal Free Hospital, London, UK and Prof. Cristina Ferrone from the Massachusetts General Hospital, Boston, USA.

The **Co-Investigator** is Dr. Dimitri Aristotle Raptis.

The complete list of the PancreasGroup.org Team is available at https://PancreasGroup.org/team

The **Scientific Committee** Members are: Mohamed Abu Hilal, Southampton, UK; Claudio Bassi, Verona, Italy; Kevin Conlon Dublin, Ireland; Brian Davidson London, UK; Marco Del Chiaro, Colorado, USA; Christos Dervenis, Athens, Greece; Massimo Falconi, Milano, Italy; Thilo Hackert, Heidelberg, Germany; Ewen Harrison, Edinburgh, UK; Ajith Siriwardena, Manchester, UK; Martin Smith, Johannesburg, South Africa; Christopher Wolfgang, Maryland, USA. Their responsibilities include, among others overseeing and controlling the scientific part of the project and giving strategic direction and support to the members of the management committee. The Members of the Scientific Committee have approved the study design and protocol of the PancreasGroup.org Study.

The responsibilities of the members of the **Management Committee** are, among others facilitating the group's decision-making processes, distributing newsletters, announcements and invitation letters, safeguarding and applying regulations, arranging regular committee and general meetings of the group, recording decisions and tasks clearly, and providing support to the collaborators.

The **Country Leaders** are responsible for recruiting centres within their country/region. Additionally,

Auditors (data monitors) will be assigned to monitor the adherence to the protocol as well as auditing the quality of data collection of the different participating centres.

Summary

Introduction: Although mortality after pancreatic surgery has decreased significantly in specialised high-volume centres, morbidity still remains high. Complexity and extent of pancreatic operations, patient selection, centre and surgeon experience all influence postoperative outcomes. Furthermore, patients present at an older age and with more comorbidities which increase the risk of postoperative complications. The aim of PancreasGroup.org is to identify the true world-wide morbidity and mortality of pancreatic operations. The second aim is to identify modifiable risk factors to improve the outcomes after pancreatic surgery.

Eligibility: Any surgeon worldwide performing pancreatic surgery is eligible to participate in PancreasGroup.org. There are no minimum number of cases to be submitted or selection criteria for centres.

Time period and team members: Each participant may form a team of 3 members in total and each centre may have more than one team. There will be 3 months of prospective patient enrolment and 3 months follow up within a 12-month frame (Jan – Dec 2021).

Inclusion criteria: All types of pancreatic surgery will be included:

- All indications (including benign and malignant
- Open, laparoscopic or robotic.
- Elective or emergency.
- Partial or total pancreatectomies.
- Pancreatic tumour enucleations.
- Procedures with concomitant vascular or other organ resections.
- Pancreatic duct drainage procedures (e.g. Frey, Puestow, or Beger)
- Adults 18 years of age or older.

Exclusion criteria:

- Pancreas or islet cell transplantation.
- Transcutaneous or transgastric imaging-guided ablation (e.g. RFA) or electroporation (e.g. NanoKnife).
- Endoscopic (e.g. ERCP, stent or lithotripsy) procedures.
- Endoscopic transgastric and surgical necrosectomies excluded.
- Patients less than 18 years of age excluded.

Outcomes: the primary endpoint of the analysis will be 90-day mortality. Secondary endpoints will be the 90 day postoperative rates of pancreatic fistula, endocrine or exocrine insufficiency, type and Clavien-Dindo grade of complications, length of stay, hospital readmission rates, and R1/R2 resections.

Data ownership: The headquarters at the Royal Free Hospital in London, UK will act as the custodian of the data. The Scientific and Management committees together will decide after the publication of the main report about requests regarding secondary analysis and will consider all such requests based on quality and the validity of the proposed project and decide by majority decision. All participants will be able to download their own submitted data in excel format without any need for permission from the study sponsor.

Authorship: A single analysis and reporting without hierarchical authorship (no first author, no last author) is planned at the end of the study (a “pure” group author publication) to reflect the collaborative effort, in keeping with other global snapshot studies. All **collaborators** will be **PubMed cited** in the main publication as well as in any future studies. Spin-off studies may include formal authorship but must include the “PancreasGroup.org Collaborative” citing all participants.

Full protocol: The complete version of the PancreasGroup.org protocol is available at: https://PancreasGroup.org/protocol

Introduction

Background/rationale

The safety of pancreatic operations has improved over the last 2 decades and has been validated by numerous studies (1-4). As a result of improved patient selection, surgical expertise and standardized postoperative care, mortality rates have decreased dramatically with rates as low as 0 to 3% reported by high-volume centres (4). Nonetheless, despite pancreatic surgery being most commonly performed by experienced surgeons in the field, the associated morbidity rates remain as high as 30 to 50% (5). The most common post-pancreatic surgery complications include postoperative pancreatic fistula (POPF), intra-abdominal abscesses and haemorrhage, which are accordingly associated with high mortality rates (6, 7). A plethora of risk factors have been identified over the years to predispose patients to postoperative complications including age, American Society of Anaesthesiology (ASA) classification, diabetes mellitus, poor nutritional status, blood loss, perioperative transfusion and pancreas texture at surgery (7). Moreover, it is accepted that the respective complexity and extent of pancreatic surgery, along with both centre and surgeon experience have a significant impact on outcomes following pancreatic operations (8, 9).

Objectives

The objective of the International Pancreatic Surgery Outcomes Study – PancreasGroup.org is to record and evaluate the current worldwide practice patterns, morbidity and mortality of pancreatic surgery, as well as identifying modifiable risk factors of outcomes after pancreatic surgery. Such will be pursued by recruiting the largest possible number of international centers, by committing to consecutive patient registration per surgeon and rigorous data validation.

The primary endpoint of the analysis will be 90-day mortality. Secondary endpoints will be pancreatic fistula and complication rates, length of stay, incidence of re-hospitalisation, R1/R2 resections, endocrine or exocrine insufficiency at 90 days postoperatively. Additionally, this snapshot study will aim to evaluate which surgical techniques are most commonly used worldwide and their impact on short-term outcomes, the use of fistula risk scores and their impact on surgical decision-making as well as the effect of perioperative measures used for the prevention of pancreatic fistula (stent, octreotide/somatostatin analogues, type of drain etc.). Furthermore, PancreasGroup.org will aim to evaluate outcomes following concurrent vascular resections during pancreatectomy. Finally, the diffusion of minimally invasive approaches in pancreatic surgery and comparison to the traditional open approach will also be evaluated.

Methods

Study design

This snapshot study is a novel form of collaborative research, which aims to provide insights into current pancreatic surgical practice by generating a population-based overview.
Other previously conducted similar snapshot studies include The International Liver Surgery Outcomes Study (LiverGroup.org), which aimed to measure the true worldwide practice of Liver surgery and associated outcomes, the International Surgical Outcomes Study (ISOS.org.uk), which recorded information about patients undergoing surgery and the care they receive and GlobalSurg 1 (GlobalSurg.org), which recorded outcomes of emergency surgery in high, middle and low income countries.

Setting

This will be an International Pancreas Surgery Outcomes Study where all centres performing pancreatic surgery worldwide will be able to participate. The current preliminary list of study sites is available at https://PancreasGroup.org/. The enrolment period will last 3 months at any time within the 12-month enrolment time frame: 1st of January 2021 until the 31st of December 2021. The Management Committee may decide to prolong the patient enrolment if deemed necessary
Data will be entered directly onto the electronic CRF available at https://PancreasGroup.org/CRF which includes the unique identifier. Collaborators will keep a key list connecting the unique database identifier with the patient name in a safe place locked away under their control and their responsibility.

Participants

All surgeons around the world performing pancreatic surgery are eligible for participation in this study. There is no minimum number of cases to be submitted or selection criteria for centres. Surgeons joining PancreasGroup.org are encouraged to propose a country or regional leader (north/south etc). The management committee will guide this process. The responsibilities of the *Regional* and *Country Leaders* representing each country in the world include, among others to recruit and co-ordinate collaborators in their own country or region as well as to provide additional scientific and administrative support to their collaborators. Additionally, personal contacts of the PancreasGroup.org team will be used to recruit centres. Furthermore, the members of the Management Committee are seeking endorsement by the International Hepato-Pancreato- Biliary Association (IHPBA), European-African Hepato-Pancreato-Biliary Association (E-AHPBA), the American Hepato-Pancreato-Biliary Association (AHPBA), the Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA), the European Pancreas Club (EPC), the American Pancreatic Society (APC), the International Association of Pancreas (IAP) and the Pancreatic Society of Great Britain and Ireland (PSGBI).

Eligibility Criteria

All patients undergoing pancreatic resection by single surgeons at their respective centres are eligible for study inclusion. The inclusion criteria are patients 18 years of age or older, any indication for an operation, including benign and malignant lesions, open, laparoscopic, hybrid or robotic approaches. Furthermore, any extent of pancreatic resection is included, from partial or total pancreatectomy to pancreatic tumour enucleation, pancreatic resections with concomitant vascular or other organ resection, pancreatic duct drainage procedure (e.g. Frey, Puestow, or Beger). The exclusion criteria are patients less than 18 years of age, pancreas or islet cell transplantation, percutaneous or transgastric imaging-guided ablation (e.g. RFA) or electroporation (e.g. NanoKnife), endoscopic (e.g. ERCP, stent or lithotripsy) procedures as well as endoscopic or surgical pancreatic necrosectomies. A minimum of 3 months period is required for follow-up of each patient.

Variables, Data sources and measurement

A detailed list of variables and their definition will be available at https://PancreasGroup.org/CRF. With regards to the quality of the collected data, the electronic CRF found on https://PancreasGroup.org is designed to force data entry for the important variables (e.g. comorbidities, procedure type, morbidity, mortality, etc.) and has minimum and maximum allowed values in order to avoid typing errors for continuous variables. All categorical data are captured in the form of selection lists whilst there is a description for important variables within the CRF. Calculators will be available at PancreasGroup.org (i.e. conversion of lab values or weight/height) in order to ensure uniform data capture. Information regarding the ISGPF, TNM Classification, AJCC Staging and Clavien-Dindo Classification will also be available at PancreasGroup.org.

Bias

Several bias adherents to the study will be addressed; any operation may not run the expected course in some patients or may be aborted or changed in scope due to specific intraoperative findings. These patients will also be recorded in the registry following the principle of intent-to treat to avoid selective reporting. Furthermore the audit process will ensure morbidity and mortality are accurately recorded. Additionally our study will recruit consecutive patients from every center thus overcoming selection and attrition bias.

Study size

The study aims for the maximum number of patients to recruit and has no power calculation for specific outcomes. Assuming a 3% 90-day mortality rate with a 50% as a clinically relevant reduction in any type of comparisons, at least 3000 patients will have to be recruited in order to be able to perform a meaningful multivariate analysis on independent risk factors for postoperative mortality.

Statistical methods

Descriptive and exploratory statistics will be performed. Continuous variables will be compared with the Student t test, the Mann-Whitney U test and the Kruskal-Wallis H test or one-way ANOVA as appropriate. Differences among proportions derived from categorical data will be compared using the Fisher or the Pearson chi-square tests as appropriate. Univariate analysis will be performed to test factors associated with postoperative outcomes. Multivariable regression models will be used to identify factors independently associated with outcomes and to adjust for differences in confounders. The results of the multivariable analyses will be reported as adjusted odds ratios (OR) with 95% confidence intervals. ROC curves and the Youden's index will be used to identify optimal cut-off points for continuous variables. All p values will be 2-sided and considered statistically significant if $p<0.05$. Missing data from not mandatory to submission fields will be clearly reported. Cases with incomplete data regarding morbidity or mortality will be excluded from the analysis and the number of those will be reported. Statistical analysis will be performed using R version 3.3.2 (R Core Team, GNU GPL v2 License), R Studio version 1.0.44 (RStudio, Inc. GNU Affero General Public License v3, Boston, MA, 2016) with the graphical user interface (GUI) rBiostatistics.com (rBiostatistics.com, London, UK, 2017).

Discussion

Pancreatic surgery has been traditionally regarded as one of the most challenging and highe-risk operations in general and visceral surgery. While they are currently regarded as safe and feasible procedures by experienced surgeons due to the significant advances over the past decades, the associated morbidity remains significant (1, 7, 10). The majority of published studies however derive from high volume centres and thus our knowledge of true rates of morbidity and mortality outside these centres remains limited. By assessing one of the largest prospective cohorts to date, which addresses surgeons around the world regardless of their annual pancreatic surgery case volume, this study will aim to evaluate whether the worldwide mortality after pancreatic surgery is indeed as low as reported in literature and furthermore investigate potential confounders associated with increased rates. Through this prospective, international, multicentre collaborative work, fields in which pancreatic surgery can be improved will be potentially better delineated and serve as a springboard for future research. Additionally, the deriving outcomes can help unify pancreatic surgery management and lead to a critical update of currently used risk assessment tools, national and international guidelines with the ultimate goal of further improving patient outcomes.

Other

Funding

PancreasGroup.org is currently supported by Fiorina Royal Free Charity, London, UK which has no influence on the study design and any future analyses and interpretation of the results. The Investigators are currently seeking for additional funding resources to support PancreasGroup.org

Monitoring

The management committee will monitor the export database of all CRFs monthly. All participating centres will undergo on-site peer-monitoring prior to final analysis. **Auditors** (data monitors), from other disciplines rather than surgery, will be assigned to monitor the adherence to the protocol as well as auditing the quality of data collection of the different participating centres.

Safety

This trial involves no risk of bodily harm to patients or investigators. Therefore, adverse events will not be monitored or reported. Data confidentiality will be protected through local anonymization. Anonymization will be monitored and breaches of confidentiality reported. Individual participants are responsible toward their local authorities for breaches in confidentiality.

Research ethics approval

The Chief investigator in the UK must ensure the recording of data is carried out in accordance with the Research Governance Framework for Health and Social Care; Second Edition, 2005, and its subsequent amendments. The principle investigators in the respective countries must clarify the need for ethics and other regulatory approvals and ensure these are in place prior to data collection. Since this study is effectively a large-scale international clinical audit of anonymized data already recorded in the course of routine patients care, we expect that in most countries no individual patient consent will be required. For countries where individual consent is required, we will provide an informed consent form in English that may be adjusted to local requirements. The English version of the patient information and consent form is available at https://PancreasGroup.org. The Management Committee Members of PancreasGroup.org will support all surgeons with their respective institutional review boards/ethics committee applications. PancreasGroup.org has been recognised as an international audit in the UK and does not require any formal ethics approval.

Declaration of interests

There are currently no financial and other competing interests of the investigators for the overall trial and each study site.

Access to data and dissemination policy

PancreasGroup.org is a collaboration of all surgeons contributing data as equal partners. Each surgeon contributing data has access to analysis files of the entire database at any time point and the right to propose analyses and publish data as long as every surgeon contributing data are included as a group author in every publication and have an opportunity to review the data prior to submission. Each collaborator has access to their own data in a form of excel export file without requiring permission or approval by the PancreasGroup.org management committee.

Authorship

A single analysis without hierarchical authorship (no first author, no last author) is planned at the end of the study (a “pure” group author publication) to reflect the collaborative effort. All members of the group are encouraged to step forward with suggested secondary analyses on specific questions and will be granted full access to the acquired data once their proposal is approved by the Scientific Committee. There will be no need for approval of publication of data from The PancreasGroup.org collaborative, however all group authors will have the right to review the manuscripts and will be given at least 1 week to be able to review the manuscripts.

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