BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054138
Article Type:	Protocol
Date Submitted by the Author:	04-Jun-2021
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Keywords:	Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Adult surgery < SURGERY

Protocol of a prospective study investigating the association of pancreatic PArenchymal RISk factors with postoperative pancreatic fistula after partial pancreaticoduodenectomy (PARIS trial)

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Word count: 3636

Abstract

Introduction: Partial Pancreatoduodenectomy (PD) is the treatment of choice for many malignant and benign diseases of the pancreatic head. Postoperative complication rates of up to 40% are regularly reported. One of the most common and potentially life-threatening complication is the postoperative pancreatic fistula (POPF). Parenchymal risk factors like main pancreatic duct diameter or texture of the pancreatic gland have already been identified in retrospective studies. The aim of this study is to evaluate the diagnostic value of parenchymal risk factors on POPF in a prospective manner.

Methods and analysis: All patients scheduled for elective PD at the Department of General, Visceral and Transplantation Surgery of the University of Heidelberg will be screened for eligibility. As diagnostic factors, diameter and texture of the pancreatic gland as well as radiological and histopathological features will be recorded. Furthermore, the new four class risk classification system by the International Study Group of Pancreatic Surgery (ISGPS) will be recorded. The postoperative course will be monitored prospectively. The primary endpoint will be the association of the main pancreatic duct size and the texture of the pancreatic gland on POPF according to the updated ISGPS definition. The diagnostic value of the above-mentioned factors for POPF will be evaluated in a univariable and multivariable analysis.

Ethics and dissemination: PARIS is a monocentric, prospective, diagnostic study to evaluate the association of parenchymal risk factors and the development of POPF approved by the Ethics Committee of the medical faculty of Heidelberg University (S-344/2019). Results will be available in 2022 and will be published at national and international meetings. With this knowledge, the intra- and perioperative decision-making process could be eased and improve the individual outcome of patient.

Trial registration number: DRKS00017184

Keywords: pancreas, surgical procedures, general surgery, pancreaticoduodenectomy, pancreatic ducts

Strength and limitations of this study
- A strength of this study is its prospective design and the application of valid applicable definitions for the main endpoints. - In this trial the texture of the pancreatic gland is measured with all known methods including haptic, radiological and pathological measurement as well as the usage of a durometer. - The trial is based on the results of a recently published systematic review investigating the association of pancreatic parenchymal risk factors with POPF. - This trial is the first study investigating and validating the recently established ISPGS pancreatic parenchymal and main pancreatic duct size classification in a prospective design. - A limitation of this trial is the monocentric design at the university hospital Heidelberg with the well-known issue of a compromised external validation.

Background

Partial Pancreatoduodenectomy (PD) is the treatment of choice for numerous malignant and benign disease of the pancreas. Although postoperative mortality after PD has decreased below 5% [1], morbidity remains high even in designated pancreatic cancer centres. Postoperative complication rates of up to 40% are regularly reported in prospective studies [2–4]. Postoperative complications have been uniformly defined by the International Study Group for Pancreatic Surgery (ISGPS) over the last decades and allows standardized reporting of postoperative pancreatic fistula (POPF) [5].

POPF is one of the most frequent PD- associated complications occurring in 15-30% of the patients [2,3,6] with a POPF related hemorrhage as possible result which represents the most severe complication after PD [1,5]. Multiple risk factors have been identified that are associated with the development of POPF following PD including patient associated risk factors like BMI [7],

perioperative risk factors and surgeon-associated risk factors (experience in PD surgery). Furthermore, a number of pancreas-associated risk factors have been proposed in the literature including histology [8], a small diameter of the main pancreatic duct (MPD) [7,9,10], soft pancreatic texture [3,11] and a excentric location of the pancreatic duct [12]. However, a prospective study assessing the diagnostic value of different parenchymal characteristics is lacking.

Pancreas-associated risk factors are clinically important as they would offer the opportunity for an easy-to-use risk classification, that might guide intraoperative and postoperative decision-making process including placement of drains, degree of resection, intensity of follow-up, need for intensive care observation, administration of somatostatin analogues and others.

Aim of the study

PARIS trial is a monocentric, prospective, diagnostic study with one study arm. The aim of this study is to evaluate the impact of MPD size and pancreatic texture as pancreas specific risk factors for the development of clinically relevant POPF. Furthermore, it aims to evaluate and validate a new four grouped parenchymal classification system including the combination of the diameter of the MPD (≤3mm vs. >3mm) and the texture of the pancreatic gland (soft, hard), in order to calculate intraoperatively the probability of a POPF during the clinical course.

Methods

The PARIS trial is a monocentric, prospective, diagnostic study with the aim to investigate the impact of the main pancreatic duct size and the parenchymal texture on the risk of a development of a POPF. According to the aim of this trial and the primary and secondary endpoints the following methodical tools were used.

Study population

Adult patients scheduled for elective PD for any indication at the department of general, visceral and transplantation surgery at the University Hospital of Heidelberg will be screened for eligibility

and will asked to participate. According to the aim of this trial all patients with the necessity of changing the surgical intervention to a total/distal pancreatectomy or no partial pancreatectomy for any reason, will be excluded for further investigations and observations.

The inclusion and exclusion criteria are illustrated in Table 1.

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
○ Scheduled for elective partial pancreaticoduodenectomy ○ Ability of subject to understand character and individual consequences of the clinical trial ○ Age ≥ 18 years ○ Written informed consent	○ Participation in an interventional trial with interference of intervention and outcome of this study ○ Patients with a legal guardian ○ Language problems

Diagnostic factors

The following diagnostic analyses will be performed in the study:

1. Preoperatively a radiologist will evaluate the density of the pancreatic parenchyma and the diameter of the MPD at the future pancreatic resection line (ventral of the superior mesenteric vein) via CT scan using the portal venous phase as imaging set.
2. A detailed histopathological investigation by an experienced pathologist will follow the surgical intervention in order to record the grade of fibrosis, lipomatous atrophy inflammatory infiltration, inflammatory activity and microscopic necrosis at the pancreatic resection margin according to the Heidelberg grading system (Table 2) [13]. The pathological work-up will be performed as published and described previously [13].

Table 2: Histological grading according to Felix et al. [13]

Grading	Fibrosis	Lipomatous atrophy	Inflammatory infiltrations	Inflammatory activity	Microscopic necrosis
0	No	No	No	No	No
1	Periductal	Little	Little	Little	Single cells
2	Periductal, intra- and interlobular	Moderate	Moderate	Moderate	Grouped necrosis
3	Extensive	Severe	Severe	Severe	Broad

3. The pancreatic texture will be measured at the pancreatic resection margin using a shore durometer (Schmidt Control Instruments, PHPSO, Hans Schmidt and Co. GmbH, Waldkreiburg, Germany) in order to get an objective recorded value of the pancreatic texture and its density measured in Shore Units (SU). The measurement will be performed as described by Belyaev et al. in 2013 [14]. Briefly, stiffness of the gland will be measured in the resected specimen at the transection line using the durometer. The mean value of three measurements at different positions on the transection line will be recorded.
4. The pancreatic texture will be evaluated by an experienced senior surgeon and classified as “soft”, “hard”, “cannot decide”.
5. The width of the MPD will be measured and recorded as well as documented with an intraoperative photograph. The classification of the diameter will be recorded as continuous variable in mm after probing the main pancreatic duct once.

6. Intraoperatively there will be a classification of the pancreatic gland according to a newly-proposed four group ISGPS pancreatic duct and texture classification system [15].

An illustration of the described classification system can be seen below (Table 3).

Table 3: Pancreatic texture and duct classification

Grade	Texture	Diameter of the MPD
A	Not-soft / hard	>3mm
B	Not-soft / hard	≤3mm
C	soft	>3mm
D	soft	≤3mm

Trial site and sample size

The trial will be performed at the Department of General, Visceral and Transplantation Surgery of the University Hospital Heidelberg. Patients will be continuously recruited until the planned trial population of 200 patients to be analysed is reached. Based on the department's data and the expected number of partial pancreaticoduodenectomies per year, the recruitment will end approximately 18 months after the first included patient, starting in January 2020. We planned a total duration of the trial of 22 months beginning with the first included patient to the final analysis of the results.

Outcomes

Due to the nature of a diagnostic trial the association of the following endpoints with the diagnostic criteria described above will be investigated.

Primary Endpoint

The primary endpoint of the study is the association of the above mentioned diagnostic factors and POPF, defined as type B and C POPF according to the ISGPS updated version of 2016 [5] within 30 days after index surgery. In order to investigate the diagnostic value of predicting a CR-POPF using pancreatic specific characteristics the positive and negative predictive value, sensitivity and specificity will be calculated. The association will be expressed by as odds ratio with corresponding 95% confidence interval and descriptive p-values.

Secondary endpoints

The same associations will be calculated for the following secondary endpoints within 30 days after index surgery:

1. Delayed gastric emptying as defined by the ISGPS [16] at visit 3,4 and 5.
2. Postpancreatectomy heamorrhage as defined by the ISGPS [17] at visit 3,4 and 5.
3. Chyle leakage as defined by the ISGPS [18] at visit 3,4 and 5.
4. Bile leakage as defined by the ISGLS [19] at visit 3,4 and 5.
5. Postoperative morbidity and mortality of the above mentioned pancreas specific or any other complications according to the Clavien-Dindo Classification [20,21] at visit 3,4 and 5.
6. Postoperative length of hospital stay (in days from index operation) at visit 4 and 5.

In addition to the above-mentioned endpoints, the following confounders will be documented:

1. Experience of surgeon (number of previously performed Whipple procedures)
2. Body Mass Index (BMI) of the patient
3. Indication for surgery (chronic pancreatitis, ductal adenocarcinoma, IPMN, neuroendocrine tumour, distal bile duct cancer, other)

4. Age (in years) of the patient
5. Type of surgical access (open vs. minimal invasive/robotic)
6. Use of somatostatin analogues
7. Prior neoadjuvant (radio-)chemotherapy
8. Preoperative total bilirubin
9. Volume and type of intraoperative intravenous fluids
10. Current medication (glucocorticoids, immunosuppressive drugs, somatostatin analogues)
11. Preoperative biliary drainage, inclusively type of the placement of the drain (endoscopic, percutaneous or operative)
12. Comorbidity according to the updated Charlson comorbidity index [22]
13. Intraoperative blood loss
14. Necessity of an arterial resection (e.g., celiac trunk, hepatic artery, superior mesenteric artery (SMA), splenic artery…)
15. Necessity of a venous resection (e.g., portal vein, superior mesenteric vein (SMV), splenic vein…)
16. Location of the pancreatic duct (ventral, centre, dorsal)
17. Degree of stomach resection (pylorus preserving, pylorus resecting, classical PD, (sub)total gastrectomy)
18. Performance of a resection of other organs which are not part of the PD (e.g., right/left hemicolon, transverse colon, spleen, segment bowel resection, partial liver resection)

Study conduct and trial visits

Visit 1

All consecutive patients are screened for potential inclusion. Eligible patients are asked for informed consent. For enrolled patients the following data items will be collected: a) demographic data; b) baseline data; c) medical history/comorbidities.

Visit 2

Visit 2 will take place in the operation theatre by an experienced senior surgeon giving detailed information about the anatomic situation before and after the surgical resection as well as the extend of resection. In addition, the following data items are collected:

1. Date of surgery
2. Typ of the surgical access (open vs laparoscopic/robotic)
3. Duration of surgery (in min, start of skin incision to end of skin closure)
4. Duration of pancreatojejunostomy (in min)
5. Estimated blood loss from the anaesthesiology report (in ml)
6. Degree of pancreatic resection, stomach resection, vascular resection with detailed description of the performed reconstruction procedures.
7. Performed triangle operation (dissection of all tissue between SMA, celiac trunk and portal vein/VMS
8. Resection of other organs (e.g., right/left hemicolon, transverse colon, partial liver resection, segment of small bowel, spleen)
9. Texture of the pancreatic gland (soft vs hard/not-soft)
10. Diameter and localization of the main pancreatic duct (MPD)
11. Insertion of abdominal drains
12. Experience of the surgeon performing the anastomosis (≤50 Whipple procedures vs > 50 Whipple procedures)

Visit 3 and 4

After the operation, the postoperative course will be observed prospectively. Visit 3 and 4 are identical, however, visit 3 will be performed on postoperative day (POD) 3-7, while visit 4 is performed on postoperative day 10-14 or at discharge, whatever comes first.

During these visits, the postoperative complications (primary and secondary endpoints) as mentioned above will be recorded and documented in the electronic case-report form (eCRF). All above mentioned complications will also be classified according to the classification system of Clavien-Dindo [20,21].

Visit 5

Visit 5 will occur on POD 30. It can be performed in person if the patient is still in hospital or returns for an outpatient visit, or via the phone. The data collection includes the identical information extracted for visit 3 and 4. Additionally, histopathological assessment will be recorded.

A detailed illustration of the study conduct and the included visits can be seen in Table 4.

Table 4: Study visits and data items.

Activity	Visit 1 (Screening, enrolment)	Visit 2 (surgery)	Visit 3 and 4 (POD 3-7 and 10-14 or at discharge) (respective visits are omitted if patient has been discharged before)	Visit 5 (POD 30)
Informed consent	X			
Eligibility criteria	X			
Demographics and baseline clinical data	X			
Density measurement from CT or MRI	X			
Surgical data		X		
Durometry		X		
Intraop. Photo documentation with ruler		X		
Assessment of primary endpoint			X	X

Assessment of secondary endpoints			X	X
Histopathology				X

Data Management

An electronic case report form (eCRF) implemented in the REDCap™ sytem [23,24] will be used for data collection. To assure a safe and secure environment for data acquired, the system used for remote data entry is validated and is compliant with FDA 21 CRF part 11. Data transmission will be encrypted with secure socket layer (SSL) technology. The database server will be located in a secure data centre and be protected by a firewall. Only authorized users will be able to enter or edit data. All changes to data will be logged with a computerized timestamp in an audit trail. All clinical data will be pseudonymized. Backups will be conducted regularly.

All data collected will be integrated in a statistical analysis system. After database closure access rights will be granted to the responsible biometrician for statistically analysis.

Statistical analysis

To investigate the primary objective of this trial, the patients will be divided into several groups according to the recorded parenchymal characteristics. Therefore, they will be dichotomised in soft and hard pancreatic texture as well as in >3mm and ≤3mm diameter of the MPD.

Furthermore, the included patients will be divided according to the allocated group of the pancreatic duct and texture classification (i.e., Group A-D).

In the next step the postoperative complications according to Clavien-Dindo, ISGPS and ISGLS will be analysed and the patients will be dichotomised weather they had a clinical relevant POPF (yes/no), if they had a POPF a more detailed differentiation will be done (Grade B or Grad C) [5].

To evaluate the primary endpoint each pancreatic parenchyma characteristic (predictor) will be evaluated for its association with POPF. Therefore, in a first step, univariate analysis will be

performed. For dichotomous, nominal and ordinal variables contingency table will be created and will be analysed by chi-square tests and Mann-Whitney unpaired two-sample tests, respectively. For continuous variables, t-tests will be performed. Furthermore, to analyse the prediction performance of each of the possible predictors and confounders, for dichotomous variables sensitivity, specificity, positive and negative predictive values will be calculated. For ordinal and continuous variables univariate logistic regression models will be used and the respective area under the curve (AUC=c-index) will be calculated. Additionally, association with POPF will be described by odds ratios with corresponding 95% confidence interval and descriptive p-values. In the same way, each of the potential confounder, as listed under “confounders” above, will be also evaluated regarding to their association with POPF.

In order to find the most important influence factors on POPF, multivariable logistic regression analysis will be performed by best subset selection and forward selection. Thereby, missing values will be imputed by multiple imputation. Variables comprised by the final model will be found in the set of predictors and confounders analysed in the univariate analyses. Assuming a prevalence of about 20% the final model will comprise up to four different predictors or confounders. The results will be summarized by AUCs, odds ratios with corresponding 95% confidence interval and descriptive p-values.

Secondary endpoints will be analysed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means, SDs, medians, 1st and 3rd quartiles, minimum and maximum or absolute and relative frequencies will be reported, respectively. P-values of further statistical tests and corresponding 95% confidence intervals will be given.

Since this study is of an observational character all p-values will be interpreted in a descriptive manner without confirmatory value and p-values smaller than 0,05 are determined as significant in a descriptive sense.

Statistical analysis will be performed based on the statistic software R version >4.0.0. [25]

Quality assurance

Monitoring

Monitoring will be done to ensure compliance with the trial protocol, the principles of the Declaration of Helsinki and ICH Good Clinical Practice as well as data protection and other relevant legal aspects. Only a centralised digital monitoring via the eCRF will be conducted using plausibility checks.

Assessment of safety

The primary and secondary endpoints include all necessary safety endpoints. No additional safety analysis will be performed in the PARIS study. For clinical trials according to Medical Association's professional code (Berufsordnung der Bundesärztekammer) § 15 no specific SAE management is required.

Methods for minimising bias

Minimising selection bias

All patients will be consecutively screened and if found to be eligible, informed consent will be obtained. The amount of screened, included, and analysed patients will be reported as well as the number of patients who were subsequently excluded or the participation of the trial was determined. For all differences there will be detailed explanations.

Minimizing performance and detection bias

Data capturing on pancreatic parenchyma characteristics and outcome assessment will be performed by two different investigators. Postoperative clinical investigators of the clinical course will be blinded to the intraoperative results, as well as the investigating radiologists and pathologist. Statistical analysis will be performed by a biometrician after closure of database.

Minimizing attrition bias

Statistical measurements such as imputation will be taken to minimize risk of bias due to incomplete outcome data [26]. The trial will be reported according to the updated Standards for Reporting of Diagnostic Accuracy (STARD) statement [27]. The trial is registered with *Deutsches Register Klinischer Studien* (DRKS). To avoid the risk of selective reporting, the trial protocol with full information about end points and profound explanation of planned statistical analysis is hereby published according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement where appropriate [28].

Minimizing other bias

Any financial relationship or any conflict of interest that could influence the work within this project will be named specifically. Confounding will be minimized by the inclusion of covariates and factors in the statistical analysis of the primary end point as mentioned in the statistical analysis section described previously.

Ethics and informed consent

The present trial will be conducted in accordance with the "Ethical principles for medical research involving human subjects" of the 18th World Medical Association General Assembly in Helsinki (1964), the Declaration of Helsinki in its actual version [29], the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), German state and national laws and regulations for data protection and the German Medical Association's Code of Conduct.

As recommended in the professional code for physicians in Germany (§15 BOÄ) the protocol pf this trial has been reviewed and approved by the Ethics Committee of the medical faculty of the University of Heidelberg before the trial started or this paper was published (S-344/2019). Any amendments will be re-evaluated and approved by the responsible independent ethics committees.

Before any patient is included in this trial a detailed conversation between a surgeon and the patient will take place in which all information (e.g., aims, conflicts, conduct, duration, possibility of termination of the participation without naming any reasons, possibility of the deletion of all gathered data in the case of a termination of the participation, methods, possible benefits and risks) will be discussed. These information will be shared in oral as well as written form.

The patients free will to be part of the trial will be documented by signature on the informed consent form. All patient related data is subject to medical confidentiality to the Federal Data Protection Act. All data transfers will be done by using pseudonyms. Third parties will not have any insight in original data.

Discussion

The PARIS trial is a monocentric, prospective, diagnostic trial with one arm and the aim to investigate the diagnostic value of different parenchymal characteristics including the pancreatic texture, the diameter of the MPD and their combination as prediction factors of a clinically relevant postoperative pancreatic fistula (CR-POPF). These results should help to validate a newly developed simple 4-stageed classification system (Table 3). This classification system in turn, aims to help reporting and intraoperative decision-making, especially concerning the extent of the resection procedure, the way of reconstruction, the necessity of abdominal drains and the need of observation on an intensive care unit or further medication.

The results will also be used to evaluate the new classification system of pre- / and intraoperatively measured parenchymal characteristics in order to estimate the risk of a CR-POPF during the clinical course. This new classification system has four groups including the most important parenchymal risk factors (texture and diameter of the MPD) in combination. The classification system is based on the results of a systematic review [15]. The results of this systematic review showed a significant association of a soft pancreatic gland and a small main pancreatic duct with the development of a clinically relevant postoperative pancreatic fistula. In sum the classification

system is based on retrospective data sets but needs more trials, especially in a prospective design to be evaluated.

Another strength of this prospective trial, next to its design, will be the objective evaluation of the pancreatic texture. Not only the haptic evaluation of a senior surgeon will be used, but there will be radiological and histopathological diagnostics, too. These methods, and the usage of a durometer to get objective results of the density of the pancreatic texture, compared to the assessment of the senior surgeon, allow representative results for the parenchymal characteristics and therefor valid investigations of the association of parenchymal risk factors with clinically relevant POPF.

As limitation of this trial can be seen that it will be performed as a single center study at the University Hospital Heidelberg, which is high-volume pancreatic center. Therefore, external validity might be compromised and the results might not be representative. However, because of the large volume and the broad and heterogeneous population at our center, generalizability of results is ensured.

According to the aim of this trial the main focus is placed on the association of pancreatic gland characteristics on the risk of developing a clinically relevant POPF, which results in another limitation of this trial, as other risk factors described in several fistula risk scores are not equally analysed. Nevertheless, parameters of the alternative fistula risk score [7] or the original fistula risk score [30] are included as confounders in this trial. Therefore, the impact of these risk factors can be investigated and they will be included in multivariate analyses.

In sum the design of this trial and the included population make it possible to work off the existing relevant lack of studies investigating the association of parenchymal risk factors and the development of a postoperative pancreatic fistula in a prospective study design.

Patient and public involvement

No patient involved.

Contributorship statement

FS, MAF, MF, MWB, ALM and PP developed the trial concept and wrote the protocol as well as the manuscript of the protocol publication. CE, CD-H, PK and MKD helped to develop the trial concept and revised the manuscript critically for important intellectual content. All listed authors approved the final version of the manuscript for publication and agreed to be accountable for all aspects of the work.

Funding

This is an investigator-initiated trial and no external funding is available.

Competing interests

All authors declare to have no competing interests that could possibly compromise the outcome of the trial.

Acknowledgements

There is no funding source available for this trial, nevertheless the resources and facilities available at the University Hospital of Heidelberg are available for conducting the trial.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	n.a
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	3,4
Objectives	7	Specific objectives or hypotheses	3,4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4,5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4,5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4,5,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4,5,7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4,5,7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4,5,7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13,14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13,14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13,14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12,14,16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14,16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10,14-16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol of a prospective study investigating the association of pancreatic PArenchymal RISk factors with postoperative pancreatic fistula after partial pancreaticoduodenectomy (PARIS trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054138.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Feb-2022
Complete List of Authors:	Schuh, Fabian; Heidelberg University, Department of General, Visceral and Transplantation Surgery Fink, Matthias; Heidelberg University, Department for Diagnostic and Interventional Radiology Feisst, Manuel; Heidelberg University, Institute of Medical Biometry and Informatics Eckert, Christoph; Heidelberg University, Institute of Pathology Dörr-Harim, Colette; Heidelberg University, Department of General, Visceral and Transplantation Surgery Knebel, Phillip; Heidelberg University, Department of General, Visceral and Transplantation Surgery Diener, M. K.; Heidelberg University, Department of General, Visceral and Transplantation Surgery Büchler, M.W.; Heidelberg University, Department of General, Visceral and Transplantation Surgery Mihaljevic, A; Heidelberg University, Department of General, Visceral and Transplantation Surgery Probst, Pascal; Heidelberg University, Department of General, Visceral and Transplantation Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery, Oncology, Gastroenterology and hepatology
Keywords:	Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Adult surgery < SURGERY

Protocol of a prospective study investigating the association of pancreatic PArenchymal RISk factors with postoperative pancreatic fistula after partial pancreaticoduodenectomy (PARIS trial)

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Word count: 3805

Abstract

Introduction: Partial Pancreatoduodenectomy (PD) is the treatment of choice for many malignant and benign diseases of the pancreatic head. Postoperative complication rates of up to 40% are regularly reported. One of the most common and potentially life-threatening complication is the postoperative pancreatic fistula (POPF). Parenchymal risk factors like main pancreatic duct diameter or texture of the pancreatic gland have already been identified in retrospective studies. The aim of this study is to evaluate the diagnostic value of parenchymal risk factors on POPF in a prospective manner.

Methods and analysis: All patients scheduled for elective PD at the Department of General, Visceral and Transplantation Surgery of the University of Heidelberg will be screened for eligibility. As diagnostic factors, diameter and texture of the pancreatic gland as well as radiological and histopathological features will be recorded. Furthermore, the new four class risk classification system by the International Study Group of Pancreatic Surgery (ISGPS) will be recorded. The postoperative course will be monitored prospectively. The primary endpoint will be the association of the main pancreatic duct size and the texture of the pancreatic gland on POPF according to the updated ISGPS definition. The diagnostic value of the above-mentioned factors for POPF will be evaluated in a univariable and multivariable analysis.

Ethics and dissemination: PARIS is a monocentric, prospective, diagnostic study to evaluate the association of parenchymal risk factors and the development of POPF approved by the Ethics Committee of the medical faculty of Heidelberg University (S-344/2019). Results will be available in 2022 and will be published at national and international meetings. With this knowledge, the intra- and perioperative decision-making process could be eased and improve the individual outcome of patient.

Trial registration number: DRKS00017184

Keywords: pancreas, surgical procedures, general surgery, pancreaticoduodenectomy, pancreatic ducts

Strength and limitations of this study
- A strength of this study is its prospective design and the application of valid applicable definitions for the main endpoints. - In this trial the texture of the pancreatic gland is measured with all known methods including haptic, radiological and pathological measurement as well as the usage of a durometer. - The trial is based on the results of a recently published systematic review investigating the association of pancreatic parenchymal risk factors with POPF. - This trial is the first study investigating and validating the recently established ISPGS pancreatic parenchymal and main pancreatic duct size classification in a prospective design. - A limitation of this trial is the monocentric design at the university hospital Heidelberg with the well-known issue of a compromised external validation.

Introduction and scientific background

Partial Pancreatoduodenectomy (PD) is the treatment of choice for numerous malignant and benign disease of the pancreas. Although postoperative mortality after PD has decreased below 5% [1], morbidity remains high even in designated pancreatic cancer centres. Postoperative complication rates of up to 40% are regularly reported in prospective studies [2–4]. Postoperative complications have been uniformly defined by the International Study Group for Pancreatic Surgery (ISGPS) over the last decades and allows standardized reporting of postoperative pancreatic fistula (POPF) [5].

POPF is one of the most frequent PD- associated complications occurring in 15-30% of the patients [2,3,6] with a POPF related hemorrhage as possible result which represents the most severe complication after PD [1,5]. Multiple risk factors have been identified that are associated with the development of POPF following PD including patient associated risk factors like BMI [7],

perioperative risk factors and surgeon-associated risk factors (experience in PD surgery). Furthermore, a number of pancreas-associated risk factors have been proposed in the literature including histology [8], a small diameter of the main pancreatic duct (MPD) [7,9,10], soft pancreatic texture [3,11] and a excentric location of the pancreatic duct [12]. However, a prospective study assessing the diagnostic value of different parenchymal characteristics is lacking.

Pancreas-associated risk factors are clinically important as they would offer the opportunity for an easy-to-use risk classification, that might guide intraoperative and postoperative decision-making process including placement of drains, degree of resection, intensity of follow-up, need for intensive care observation, administration of somatostatin analogues and others.

Aim of the study

PARIS trial is a monocentric, prospective, diagnostic study with one study arm. The aim of this study is to evaluate the impact of MPD size and pancreatic texture as pancreas specific risk factors for the development of clinically relevant POPF. Furthermore, it aims to evaluate and validate a new four grouped parenchymal classification system including the combination of the diameter of the MPD (≤3mm vs. >3mm) and the texture of the pancreatic gland (soft, hard), in order to calculate intraoperatively the probability of a POPF during the clinical course.

Methods

The PARIS trial is a monocentric, prospective, diagnostic study with the aim to investigate the impact of the main pancreatic duct size and the parenchymal texture on the risk of a development of a POPF. According to the aim of this trial and the primary and secondary endpoints the following methodical tools were used.

Study population

Adult patients scheduled for elective PD for any indication at the department of general, visceral and transplantation surgery at the University Hospital of Heidelberg will be screened for eligibility

and will asked to participate. According to the aim of this trial all patients with the necessity of changing the surgical intervention to a total/distal pancreatectomy or no partial pancreatectomy for any reason, will be excluded for further investigations and observations.

The inclusion and exclusion criteria are illustrated in Table 1.

Table 1: Eligibility criteria

Inclusion criteria	Exclusion criteria
○ Scheduled for elective partial pancreaticoduodenectomy ○ Ability of subject to understand character and individual consequences of the clinical trial ○ Age ≥ 18 years ○ Written informed consent	○ Participation in an interventional trial with interference of intervention and outcome of this study ○ Patients with a legal guardian ○ Language problems

Diagnostic factors

The following diagnostic analyses will be performed in the study:

1. Preoperatively a radiologist will evaluate the density of the pancreatic parenchyma and the diameter of the MPD at the future pancreatic resection line (ventral of the superior mesenteric vein) via CT scan using the portal venous phase as imaging set. In case of a MPD too small to be measured radiologically, the duct diameter will be rated as 1mm.
2. A detailed histopathological investigation by an experienced pathologist will follow the surgical intervention in order to record the grade of fibrosis, lipomatous atrophy inflammatory infiltration, inflammatory activity and microscopic necrosis at the pancreatic resection margin according to the Heidelberg grading system (Table 2) [13]. The pathological work-up will be performed as published and described previously [13].

Table 2: Histological grading according to Felix et al. [13]

Grading	Fibrosis	Lipomatous atrophy	Inflammatory infiltrations	Inflammatory activity	Microscopic necrosis
0	No	No	No	No	No
1	Periductal	Little	Little	Little	Single cells
2	Periductal, intra- and interlobular	Moderate	Moderate	Moderate	Grouped necrosis
3	Extensive	Severe	Severe	Severe	Broad

3. The pancreatic texture will be measured at the pancreatic resection margin using a shore durometer (Schmidt Control Instruments, PHPSO, Hans Schmidt and Co. GmbH, Waldkreiburg, Germany) in order to get an objective recorded value of the pancreatic texture and its density measured in Shore Units (SU). The measurement will be performed as described by Belyaev et al. in 2013 [14]. Briefly, stiffness of the gland will be measured in the resected specimen at the transection line using the durometer. The mean value of three measurements at different positions on the transection line will be recorded.
4. The pancreatic texture will be evaluated by an experienced senior surgeon and classified as “soft”, “hard”, “cannot decide”.

5. The width of the MPD will be measured and recorded as well as documented with an intraoperative photograph. The classification of the diameter will be recorded as continuous variable in mm after probing the main pancreatic duct once.
6. Intraoperatively there will be a classification of the pancreatic gland according to a newly-proposed four group ISGPS pancreatic duct and texture classification system [15].

An illustration of the described classification system can be seen below (Table 3).

Table 3: Pancreatic texture and duct classification

Grade	Texture	Diameter of the MPD
A	Not-soft / hard	>3mm
B	Not-soft / hard	≤3mm
C	soft	>3mm
D	soft	≤3mm

Trial site and sample size

The trial will be performed at the Department of General, Visceral and Transplantation Surgery of the University Hospital Heidelberg. Patients will be continuously recruited until the planned trial population of 200 patients to be analysed is reached. Based on the department's data and the expected number of partial pancreaticoduodenectomies per year, the recruitment will end approximately 18 months after the first included patient, starting in January 2020. We planned a total duration of the trial of 22 months beginning with the first included patient to the final analysis of the results.

Outcomes

Due to the nature of a diagnostic trial the association of the following endpoints with the diagnostic criteria described above will be investigated.

Primary Endpoint

The primary endpoint of the study is the association of the above mentioned diagnostic factors and POPF, defined as type B and C POPF according to the ISGPS updated version of 2016 [5] within 30 days after index surgery. In order to investigate the diagnostic value of predicting a CR-POPF using pancreatic specific characteristics the positive and negative predictive value, sensitivity and specificity will be calculated. The association will be expressed by as odds ratio with corresponding 95% confidence interval and descriptive p-values.

Secondary endpoints

The same associations will be calculated for the following secondary endpoints within 30 days after index surgery:

1. Delayed gastric emptying as defined by the ISGPS [16] at visit 3,4 and 5.
2. Postpancreatectomy heamorrhage as defined by the ISGPS [17] at visit 3,4 and 5.
3. Chyle leakage as defined by the ISGPS [18] at visit 3,4 and 5.
4. Bile leakage as defined by the ISGLS [19] at visit 3,4 and 5.
5. Postoperative morbidity and mortality of the above mentioned pancreas specific or any other complications according to the Clavien-Dindo Classification [20,21] at visit 3,4 and 5.
6. Postoperative length of hospital stay (in days from index operation) at visit 4 and 5.

In addition to the above-mentioned endpoints, the following confounders will be documented:

1. Experience of surgeon (number of previously performed Whipple procedures)

2. Body Mass Index (BMI) of the patient
3. Indication for surgery (chronic pancreatitis, ductal adenocarcinoma, IPMN, neuroendocrine tumour, distal bile duct cancer, other)
4. Age (in years) of the patient
5. American Society of Anesthesiologists (ASA) Classification
6. Type of surgical access (open vs. minimal invasive/robotic)
7. Use of somatostatin analogues
8. Prior neoadjuvant (radio-)chemotherapy
9. Preoperative total bilirubin
10. Volume and type of intraoperative intravenous fluids
11. Current medication (glucocorticoids, immunosuppressive drugs, somatostatin analogues)
12. Preoperative biliary drainage, inclusively type of the placement of the drain (endoscopic, percutaneous or operative)
13. Comorbidity according to the updated Charlson comorbidity index [22]
14. Intraoperative blood loss
15. Necessity of an arterial resection (e.g., celiac trunk, hepatic artery, superior mesenteric artery (SMA), splenic artery…)
16. Necessity of a venous resection (e.g., portal vein, superior mesenteric vein (SMV), splenic vein…)
17. Location of the pancreatic duct (ventral, centre, dorsal)
18. Degree of stomach resection (pylorus preserving, pylorus resecting, classical PD, (sub)total gastrectomy)
19. Performance of a resection of other organs which are not part of the PD (e.g., right/left hemicolon, transverse colon, spleen, segment bowel resection, partial liver resection)

Study conduct and trial visits

Visit 1

All consecutive patients are screened for potential inclusion. Eligible patients are asked for informed consent. For enrolled patients the following data items will be collected: a) demographic data; b) baseline data; c) medical history/comorbidities.

Visit 2

Visit 2 will take place in the operation theatre by an experienced senior surgeon giving detailed information about the anatomic situation before and after the surgical resection as well as the extend of resection. In addition, the following data items are collected:

1. Date of surgery
2. Typ of the surgical access (open vs laparoscopic/robotic)
3. Duration of surgery (in min, start of skin incision to end of skin closure)
4. Duration of pancreatojejunostomy (in min)
5. Estimated blood loss from the anaesthesiology report (in ml)
6. Degree of pancreatic resection, stomach resection, vascular resection with detailed description of the performed reconstruction procedures.
7. Performed triangle operation (dissection of all tissue between SMA, celiac trunk and portal vein/VMS
8. Resection of other organs (e.g., right/left hemicolon, transverse colon, partial liver resection, segment of small bowel, spleen)
9. Texture of the pancreatic gland (soft vs hard/not-soft)
10. Diameter and localization of the main pancreatic duct (MPD)
11. Insertion of abdominal drains

12. Experience of the surgeon performing the anastomosis (≤50 Whipple procedures vs > 50 Whipple procedures)

Visit 3 and 4

After the operation, the postoperative course will be observed prospectively. Visit 3 and 4 are identical, however, visit 3 will be performed on postoperative day (POD) 3-7, while visit 4 is performed on postoperative day 10-14 or at discharge, whatever comes first.

During these visits, the postoperative complications (primary and secondary endpoints) as mentioned above will be recorded and documented in the electronic case-report form (eCRF). All above mentioned complications will also be classified according to the classification system of Clavien-Dindo [20,21].

Visit 5

Visit 5 will occur on POD 30. It can be performed in person if the patient is still in hospital or returns for an outpatient visit, or via the phone. The data collection includes the identical information extracted for visit 3 and 4. Additionally, histopathological assessment will be recorded.

A detailed illustration of the study conduct and the included visits can be seen in Table 4.

Table 4: Study visits and data items.

Activity	Visit 1 (Screening, enrolment)	Visit 2 (surgery)	Visit 3 and 4 (POD 3-7 and 10-14 or at discharge) (respective visits are omitted if patient has been discharged before)	Visit 5 (POD 30)
Informed consent	X			
Eligibility criteria	X			
Demographics and baseline clinical data	X			
Density measurement from CT or MRI	X			
Surgical data		X		

Durometry		X		
Intraop. Photo documentation with ruler		X		
Assessment of primary endpoint			X	X
Assessment of secondary endpoints			X	X
Histopathology				X

Data Management

An electronic case report form (eCRF) implemented in the REDCap™ sytem [23,24] will be used for data collection. To assure a safe and secure environment for data acquired, the system used for remote data entry is validated and is compliant with FDA 21 CRF part 11. Data transmission will be encrypted with secure socket layer (SSL) technology. The database server will be located in a secure data centre and be protected by a firewall. Only authorized users will be able to enter or edit data. All changes to data will be logged with a computerized timestamp in an audit trail. All clinical data will be pseudonymized. Backups will be conducted regularly.

All data collected will be integrated in a statistical analysis system. After database closure access rights will be granted to the responsible biometrician for statistically analysis.

Statistical analysis

To investigate the primary objective of this trial, the patients will be divided into several groups according to the recorded parenchymal characteristics. Therefore, they will be dichotomised in soft and hard pancreatic texture as well as in >3mm and ≤3mm diameter of the MPD. If the pancreatic texture was classified as “cannot decide” intraoperatively, the patients will be excluded for the primary analysis. For sensitivity analyses this group of patients will be added to the soft as well as to the hard texture group.

Furthermore, the included patients will be divided according to the allocated group of the pancreatic duct and texture classification (i.e., Group A-D).

In the next step the postoperative complications according to Clavien-Dindo, ISGPS and ISGLS will be analysed and the patients will be dichotomised weather they had a clinical relevant POPF (yes/no), if they had a POPF a more detailed differentiation will be done (Grade B or Grade C) [5].

To evaluate the primary endpoint each pancreatic parenchyma characteristic (predictor) will be evaluated for its association with POPF. Therefore, in a first step, univariate analysis will be performed. For dichotomous, nominal and ordinal variables contingency table will be created and will be analysed by chi-square tests. For continuous variables, t-tests will be performed. Furthermore, to analyse the prediction performance of each of the possible predictors and confounders, for dichotomous variables sensitivity, specificity, positive and negative predictive values will be calculated. For ordinal and continuous variables univariate logistic regression models will be used and the respective area under the curve (AUC=c-index) will be calculated. Additionally, association with POPF will be described by odds ratios with corresponding 95% confidence interval and descriptive p-values. In the same way, each of the potential confounder, as listed under “confounders” above, will be also evaluated regarding to their association with POPF.

In order to find the most important influence factors on POPF, multivariable logistic regression analysis will be performed by best subset selection and forward selection (based on the Akaike information criterion (AIC)). Thereby, missing values will be imputed by multiple imputation. Variables comprised by the final model will be found in the set of predictors and confounders analysed in the univariate analyses. Assuming a prevalence of about 20% the final model will comprise up to four different predictors or confounders. The results will be summarized by AUCs, odds ratios with corresponding 95% confidence interval and descriptive p-values. Based on the sample size of n=200, the resulting widths of the confidence intervals calculated in the models are 13.1% (based on an AUC value of 0.8).

If there will be enough patients having a POPF Grade C [5] as postoperative complication, a subgroup analysis discriminating CR-POPF Grade B and C [5] will be performed.

Secondary endpoints will be analysed descriptively by tabulation of the measures of the empirical distributions. According to the scale level of the variables, means, SDs, medians, 1st and 3rd quartiles, minimum and maximum or absolute and relative frequencies will be reported, respectively. P-values of further statistical tests and corresponding 95% confidence intervals will be given.

Since this study is of an observational character all p-values will be interpreted in a descriptive manner without confirmatory value and p-values smaller than 0,05 are determined as significant in a descriptive sense.

Statistical analysis will be performed based on the statistic software R version >4.0.0. [25]

Quality assurance

Monitoring

Monitoring will be done to ensure compliance with the trial protocol, the principles of the Declaration of Helsinki and ICH Good Clinical Practice as well as data protection and other relevant legal aspects. Only a centralised digital monitoring via the eCRF will be conducted using plausibility checks.

Assessment of safety

The primary and secondary endpoints include all necessary safety endpoints. No additional safety analysis will be performed in the PARIS study. For clinical trials according to Medical Association's professional code (Berufsordnung der Bundesärztekammer) § 15 no specific SAE management is required.

Methods for minimising bias

Minimising selection bias

All patients will be consecutively screened and if found to be eligible, informed consent will be obtained. The amount of screened, included, and analysed patients will be reported as well as the number of patients who were subsequently excluded or the participation of the trial was determined. For all differences there will be detailed explanations.

Minimizing performance and detection bias

Data capturing on pancreatic parenchyma characteristics and outcome assessment will be performed by two different investigators. Postoperative clinical investigators of the clinical course will be blinded to the intraoperative results, as well as the investigating radiologists and pathologist. Statistical analysis will be performed by a biometrician after closure of database.

Minimizing attrition bias

Statistical measurements such as imputation will be taken to minimize risk of bias due to incomplete outcome data [26]. The trial will be reported according to the updated Standards for Reporting of Diagnostic Accuracy (STARD) statement [27]. The trial is registered with *Deutsches Register Klinischer Studien* (DRKS). To avoid the risk of selective reporting, the trial protocol with full information about end points and profound explanation of planned statistical analysis is hereby published according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement where appropriate [28].

Minimizing other bias

Any financial relationship or any conflict of interest that could influence the work within this project will be named specifically. Confounding will be minimized by the inclusion of covariates and factors in the statistical analysis of the primary end point as mentioned in the statistical analysis section described previously.

Ethics and Dissemination

The present trial will be conducted in accordance with the "Ethical principles for medical research involving human subjects" of the 18th World Medical Association General Assembly in Helsinki (1964), the Declaration of Helsinki in its actual version [29], the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), German state and national laws and regulations for data protection and the German Medical Association's Code of Conduct.

As recommended in the professional code for physicians in Germany (§15 BOÄ) the protocol of this trial has been reviewed and approved by the Ethics Committee of the medical faculty of the University of Heidelberg before the trial started or this paper was published (S-344/2019). Any amendments will be re-evaluated and approved by the responsible independent ethics committees.

Before any patient is included in this trial a detailed conversation between a surgeon and the patient will take place in which all information (e.g., aims, conflicts, conduct, duration, possibility of termination of the participation without naming any reasons, possibility of the deletion of all gathered data in the case of a termination of the participation, methods, possible benefits and risks) will be discussed. These information will be shared in oral as well as written form.

The patients free will to be part of the trial will be documented by signature on the informed consent form. All patient related data is subject to medical confidentiality to the Federal Data Protection Act. All data transfers will be done by using pseudonyms. Third parties will not have any insight in original data.

Data Sharing

All data of individual patients will be shared in an anonymous form upon reasonable request.

Discussion

The PARIS trial is a monocentric, prospective, diagnostic trial with one arm and the aim to investigate the diagnostic value of different parenchymal characteristics including the pancreatic texture, the diameter of the MPD and their combination as prediction factors of a clinically relevant postoperative pancreatic fistula (CR-POPF). These results should help to validate a newly developed simple 4-stageed classification system (Table 3). This classification system in turn, aims to help reporting and intraoperative decision-making, especially concerning the extent of the resection procedure, the way of reconstruction, the necessity of abdominal drains and the need of observation on an intensive care unit or further medication.

The results will also be used to evaluate the new classification system of pre- / and intraoperatively measured parenchymal characteristics in order to estimate the risk of a CR-POPF during the clinical course. This new classification system has four groups including the most important parenchymal risk factors (texture and diameter of the MPD) in combination. The classification system is based on the results of a systematic review [15]. The results of this systematic review showed a significant association of a soft pancreatic gland and a small main pancreatic duct with the development of a clinically relevant postoperative pancreatic fistula. In sum the classification system is based on retrospective data sets but needs more trials, especially in a prospective design to be evaluated.

Another strength of this prospective trial, next to its design, will be the objective evaluation of the pancreatic texture. Not only the haptic evaluation of a senior surgeon will be used, but there will be radiological and histopathological diagnostics, too. These methods, and the usage of a durometer to get objective results of the density of the pancreatic texture, compared to the assessment of the senior surgeon, allow representative results for the parenchymal characteristics and therefor valid investigations of the association of parenchymal risk factors with clinically relevant POPF.

As limitation of this trial can be seen that it will be performed as a single center study at the University Hospital Heidelberg, which is high-volume pancreatic center. Therefore, external

validity might be compromised and the results might not be representative. However, because of the large volume and the broad and heterogeneous population at our center, generalizability of results is ensured.

According to the aim of this trial the main focus is placed on the association of pancreatic gland characteristics on the risk of developing a clinically relevant POPF, which results in another limitation of this trial, as other risk factors described in several fistula risk scores are not equally analysed. Nevertheless, parameters of the alternative fistula risk score [7] or the original fistula risk score [30] are included as confounders in this trial. Therefore, the impact of these risk factors can be investigated and they will be included in multivariate analyses.

Another limitation of this trial is that due to a lack of clear data regarding the impact of the investigated risk factors and, especially the combination of those factors, an adequate diagnostic sample size calculation was not possible at this time, as there is no data on the new ISGPS classification yet. Therefore, more studies investigating the issue of this trial will be needed.

In sum the design of this trial and the included population make it possible to work off the existing relevant lack of studies investigating the association of parenchymal risk factors and the development of a postoperative pancreatic fistula in a prospective study design.

Patient and public involvement

No patient involved.

Contributorship statement

FS, MAF, MF, MWB, ALM and PP developed the trial concept and wrote the protocol as well as the manuscript of the protocol publication. CE, CD-H, PK and MKD helped to develop the trial concept and revised the manuscript critically for important intellectual content. All listed authors approved the final version of the manuscript for publication and agreed to be accountable for all aspects of the work.

Funding

This is an investigator-initiated trial and received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

All authors declare to have no competing interests that could possibly compromise the outcome of the trial.

Acknowledgements

There is no funding source available for this trial, nevertheless the resources and facilities available at the University Hospital of Heidelberg are available for conducting the trial.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	n.a
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3,4
	6b	Explanation for choice of comparators	3,4
Objectives	7	Specific objectives or hypotheses	3,4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	4,5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5-7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4,5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4,5,7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4,5,7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4,5,7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4,5,7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13,14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13,14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13,14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-15
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13-16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12,14,16
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	14,16
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10,14-16
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.