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Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial

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- **Title:**

Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial.

- **Author names and affiliations**

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- **Structured abstract:**

Introduction: Postoperative pancreatic fistula (POPF) remains one of the most severe complications of laparoscopic pancreaticoduodenectomy (LPD). Theoretically, the level of pancreatic transection can significantly affect the occurrence of POPF by influencing both the blood supply and the location of the main pancreatic duct in the pancreatic transverse section. However, there exists no

randomised trial dedicated to answering whether patients could benefit from extended pancreatic neck transection. The level of pancreatic neck transection during LPD is not conclusive in clinical practice. Thus, we conduct this randomised trial with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

Methods and analysis: The LPDEXCEPT trial is a multicenter, randomized-controlled, open-label, superiority trial in 4 centers whose annual surgical volume for LPD is more than 25 cases with pancreatic surgeons who had completed their learning curve. A total of 154 patients who meet the inclusive and exclusive criteria are randomly allocated to the extended pancreatic neck transection group or conventional pancreatic neck transection group in a 1:1 ratio. The stratified randomised block design will be applied, with stratified factors are surgical center and the diameter of the main pancreatic duct measured by preoperative CT scan (preMPD). The primary outcome is the incidence of the clinically relevant pancreatic fistula.

Ethics and dissemination: Ethics Committee on Biomedical Research of West China Hospital of Sichuan University has approved this trial in March 2023(Approval No.2023-167). Results of this trial will be published in peer-reviewed journals and conference proceedings.

Registration details: ClinicalTrials.gov: NCT05808894

• Strengths and limitations of this study

1. The study is designed as a multicentric, randomised-controlled trial to obtain conclusion on the highest evidence level to provide the evidence concerning the possible benefits of extended pancreatic neck transection during laparoscopic pancreaticoduodenectomy, which had been registered internationally.
2. This is the first randomised trial to validate the benefits of extended pancreatic neck transection.
3. This study applied stratified randomised block design, whose stratified factors are surgical center and the diameter of the main pancreatic duct measured by the

preoperative abdominal CT scan. This will balance possible bias among research centers and pancreatic features.

4. The main limitation is that this study is carried out by a large team of researchers, including surgeons, radiologists, pathologists, data collectors, and statisticians. The coordination of this team is a big challenge.
5. LPDEXCEPT is an open-label trail, however, the primary and secondary outcomes are objective conditions which can be influenced by researchers.

• Introduction

Pancreaticoduodenectomy is the standard procedure for patients with malignant or benign tumors of the pancreatic head, the lower common bile duct, and the periampullary area of the duodenum. Since Gagner and his colleagues performed and introduced the first total laparoscopic pancreaticoduodenectomy (LPD) in 1994[1], LPD has become progressively acknowledged for its advantages such as less bleeding, less pain, and faster recovery [2-4].

Despite the advances in laparoscopic technology, postoperative pancreatic fistula (POPF) remains one of the most severe complications of LPD, which occurs in around 20% of patients [4,5]. POPF is typically associated with secondary complications, such as post-pancreatectomy hemorrhage, intra-abdominal infection. These could lead to prolonged length of hospital stay, increased hospital cost, and even death [6,7]. Therefore, prevention of POPF has always been of high priority in pancreatic surgery.

Theoretically, the level of pancreatic transection can significantly affect the occurrence of POPF by influencing both the blood supply to the anastomosis and the location of the main pancreatic duct in the pancreatic transverse section. The head of the pancreas is supplied by the anterior and posterior pancreaticoduodenal arterial arcades which are formed by branches from the celiac trunk and the superior mesenteric artery. The body and tail of the pancreas are supplied by branches from the splenic artery [8]. And there is an intermediate zone lacking proper vascularization in the neck of the pancreas, called “vascular watershed” [8]. Therefore, the level of pancreatic neck transection

might influence the pancreatic stump vascularization. Strasberg et al. have studied the impact of the defects of pancreatic stump vascularization on POPF and showed there is a statistically significant correlation [9,10]. The main pancreatic duct arises in the tail of the pancreas, and lies midway between the superior and inferior margins and slightly more posterior than anterior through the tail and body of the pancreas. Then it turns caudad and posterior on reaching the head of the pancreas [8]. Therefore, the level of pancreatic neck transection could influence the location of the main pancreatic duct in the pancreatic transverse section. Several studies had revealed the association between the location of the pancreatic duct and POPF [11,12]. And they found the risk of POPF was reduced when the center of pancreatic duct is far from the edge of pancreas.

Bardol et al. conducted a retrospective cohort study and consolidated that long remnant pancreatic neck could be an independent risk factor for POPF after pancreaticoduodenectomy [13]. However, to date, there exists no randomised trial dedicated to answering whether patients could benefit from extended pancreatic neck transection. The level of pancreatic neck transection during LPD is not conclusive in clinical practice. Thus, we conduct this multicenter randomised trial, LPDEXCEPT, with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

• Methods and analysis

We wrote this protocol in line with the Standard Protocol Item Recommendation for Interventional Trials (SPIRIT) 2013 guideline [14].

Design

The LPDEXCEPT trial was designed as a multicenter, randomised, controlled, open-label, superiority trial with two parallel groups. The broad goal of this trial is to evaluate the superiority of extended pancreatic neck transection during LPD. The primary objective of this trial is to compare the incidence of clinically relevant pancreatic fistula (CR-POPF) between the study group and the control group. And the secondary objective is to compare the incidence of postoperative morbidity (Clavien-Dindo score

≥3), the location of pancreatic duct, and the surgical performance of pancreatojejunostomy between the two groups. The flow diagram for LPDEXCEPT was shown as figure 1.

Study population

All patients with an indication for elective LPD will be evaluated. The inclusion and exclusion criteria for patients are as follows:

Participants inclusion criteria

(1) Patients with benign or resectable malignant tumors of the lower common bile duct, Vater ampulla, head or uncinate process of the pancreas.

(2) 18 years old < age < 80 years old, no gender limit.

(3) Patient is expected survival beyond 3 months.

(4) No pregnancy or pregnancy plan within 3 months after surgery.

(5) Nutrition risk score <3 according to the Nutritional Risk Screening for Inpatients 2002 (NRS2002) standard score [15].

(6) No contraindication to surgery for anesthetic evaluation.

(7) The subjects voluntarily joined the study and signed an informed consent form, with good compliance and cooperation with follow-up.

Participants exclusion criteria

(1) Patients with borderline resectable and unresectable malignancies according to the National Comprehensive Cancer Network (NCCN) and the General Office of National Health Commission clinical practice guidelines [16,17].

(2) Patients undergoing neoadjuvant chemotherapy or radiotherapy.

(3) Patients with tumors exceeding the level of the gastroduodenal artery as measured by preoperative radiography.

(4) Intraoperative exploration reveals tumor adhesions with portal vein-superior mesenteric vein, requiring revascularization and reconstruction.

(5) Operation transfers to open.

(6) Operation transfers to other procedure.

(7) The duct-to-mucosa pancreaticojejunostomy is not performed due to the main

pancreatic duct cannot be found intraoperatively.

Interventions

Study group: Extended transection group

The patients in extended transection group obtain extended pancreatic neck transection during LPD. Surgeons will transect the pancreatic neck at more than 5 mm and less than 10 mm beyond the left side of the portal vein.

Control group: Conventional transection group

The patients in conventional transection group obtain conventional pancreatic neck transection during LPD. Surgeons will transect the pancreatic neck above the mesenteric-portal axis.

Figure 2 illustrates the level of the pancreatic neck transection of the two groups.

Outcomes

Primary outcome measures

The primary outcome is the incidence of the CR-POPF according to the International Study Group of Pancreatic Surgery's (ISGPS) definition and grading [18].

Secondary Outcome Measures

The secondary outcomes include the location of the pancreatic duct in the pancreatic transverse section, the duration of pancreaticojejunostomy, postoperative morbidity, and mortality within 3 months postoperatively. The location of the pancreatic duct in the pancreatic transverse section will be measured by the way described as following: Before performing the pancreaticojejunostomy, place the pancreatic transverse section in the central position of the lens. Measure the anterior-posterior diameter of the pancreas and the distance of the pancreatic duct from the back of the pancreas. The location of the pancreatic duct in the pancreatic transverse section is equal to the ratio of the distance of the pancreatic duct from the back of the pancreas to the anterior-posterior diameter of the pancreas. Postoperative morbidity will be classified according to the Clavien-Dindo score [19].

Participating surgeons and hospital criteria

The trials will be conducted in tertiary care hospitals and academic hospitals.

Participating hospitals must satisfy that annual surgical volume for LPD is more than 25 cases, according to the consensus on LPD [20]. Participating surgeons must have completed their learning curve for LPD.

Sample size

The sample size was determined based on the primary objective of comparing the incidence of CR-POPF between the two groups. According to the retrospective study[13], extended pancreatic neck transection (≥+7mm) was associated with a lower incidence of CR-POPF than conventional pancreatic neck transection (15.4% vs. 33.3%). Considering this study is a superiority trial, using the one-sided test with 80% power (1-β) at a significance level of 5% (α), the minimal sample size needed to detect a significant difference is calculated to be 70 patients in each group. Considering the loss of follow-up and washout, we enlarged the sample size by 10%. Then, there are 77 patients in each group, and the final sample size is 154 patients.

Participant timeline.

The trial time schedule of enrolment is estimated to be a 3-year period, followed by a 3-month follow-up visit after discharge from the hospital. Once the eligibility of the patients is confirmed, randomization will be applied. The intervention will be applied intraoperatively. The assessment and visits for patients will be mandatory in the first month, and third month with either telephone or in-hospital follow-up. The participant timeline was shown in the Table 1.

Recruitment

The recruiters in each center will screen eligible patients through the outpatient department or inpatient department. The duration of the recruitment period is estimated to be a 36-month interval depending on each center's recruiting rate. No financial incentives will be provided to trial investigators or patients for enrolment in the recruitment period.

Randomization and allocation.

Stratified randomised block design with a block number of four will be applied. The

stratified factors are surgical center and the diameter of the main pancreatic duct measured by the preoperative abdominal CT scan (preMPD). According to classification made by the ISGPS [21], the patients will be stratified into preMPD ≤3 mm and preMPD > 3 mm.

A data manager generated the randomization lists by computer system. The randomization lists will not be available to surgeons, recruiters, and data collectors. And the randomization lists will be embedded in a password-protected mobile application which was created to collect and manage data by our study team. The randomization will be centralised through the mobile application. Allocation of each patient will be announced to the surgeon by the mobile application only after the assessment of baseline information of the patients and the upload of the signed informed consent.

Blinding

The patients, surgeons, data collectors, outcome assessors and data analysts are unblinded. The primary outcome of this study is the incidence of CR-POPF. The definition and the criteria of CR-POPF are objective condition and would not be influenced by the patients and surgeons even if they are unblinded. And the data collectors, outcomes assessors and the data analysts are not involved in perioperative management of the patients. Thus, they have no determination of the CR-POPF.

Data collection and management

Baseline characteristics will be recorded before randomization. Intraoperative information, histopathological information, primary outcome, and secondary outcomes will be collected after randomization from hospitalization up to 3 months postoperatively. The detailed data list was shown in the Table 1.

We have created a special mobile application to collect and manage study data. The mobile application and database are password-protect. The investigators and data collectors are to be qualified to the access the mobile application and the database. Data collection will be completed in accordance with standard specification processes. The

investigators and data collectors enter the original data into the mobile application.

Data monitoring

Data Monitoring Committee (DMC) has been established. It is not competing interests. Through the combination of our internet-based and instantaneous mobile application, the DMC will conduct data monitoring to ensure that the reported clinical study data are accurate, complete, and verifiable from source documents throughout the whole trial.

An interim analysis is performed on the primary endpoint when 50% of patients have been randomised and have completed the 3 months follow-up. The interim analysis is performed by an independent statistician. The statistician will report to the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The ethics committee decides on the continuation of the trial.

Harms

An adverse event will be defined as any untoward medical occurrence in a subject without regard to the possibility of a causal relationship. All adverse events will be collected and recorded in detail according to the Common Terminology Criteria for Adverse Events (CTCAE V.4.0) after the subject has provided consent and enrolled in the study. And the data will be collected by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University and the ClinicalTrials.gov Protocol Registration and Results System.

Protocol amendments.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. And the health authorities will be notified in accordance with local regulations.

Auditing.

Auditing will be performed per year, at 50% of the inclusions, and at the end of the study by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The auditing will be independent from investigators.

Confidentiality.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All databases will be secured with the password-protected data collection system.

Access to data.

All participating investigators will be able to access the data of the registry, perform statistical analysis, discuss the results, and write the scientific manuscripts. Project principal investigators will have direct access to their own site's data sets, and will have access to other sites data by request. Data dispersed to project team members will be blinded of any identifying participant information.

Statistical methods

Statistical analysis will be performed using IBM SPSS statistics Version 25.0 (SPSS Inc., Chicago, IL) and the R programme Version 4.2.1 (R Foundation for Statistical Computing Platform). For continuous variables following a normal distribution, results were reported as the mean ± standard deviation (SD) for the data, otherwise, the median with interquartile range (IQR) was reported. Categorical variables were reported as frequency and percentage. The two-side P value < 0.05 was considered statistically significant. The Chi-Squared test or Fisher's exact test will be used to compare the categorical data between the study group and the control group as appropriate. The independent sample T test will be used to compare the continuous variables following a normal distribution between the two groups. And the continuous non-normally distributed variables will be compared using the Mann-Whitney U test. A Logistic regression analysis will be performed to investigate predictors of CR-POPF. All variables with a p value $<$ 0.1 in a univariable analysis are included in the multivariable Logistic regression analysis.

Bias due to missing data will be investigated by comparing the baseline characteristics of participants with and without missing values. Analysis in all randomly assigned patients (intention-to-treat analysis) will be conducted as sensitivity analyses. In addition, multiple imputations will be used to impute missing data, and the imputed data will also be analyzed as part of the sensitivity analyses. The primary and secondary outcomes will also be analyzed in all eligible patients who began the protocol treatment (per-protocol population), excluding ineligible patients and those not receiving the allocated treatment from all randomly assigned patients.

• Ethics and dissemination

The ethics approval of the trial has been obtained from the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University in March 2023 (Approval No.2023-167). The ethics Committee of each participating centers had accepted the decision of ethical review of the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The English and Chinese versions of the informed consent materials were shown in Appendix 1. Trained research surgeons will introduce the trial to patients who have the indication for LPD. Patients will then be able to have an informed discussion with the participating consultant. Research surgeons will obtain written consent from patients willing to participate in the trial before entering the study.

The result of this study will be reported according to the CONSORT2010 guidelines [22]. Any study results will be published in peer-reviewed journals and conference proceedings. The results will be released to the participating physicians, referring physicians, patients, and the general medical community.

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Figure legend

Figure 1. Flow diagram for LPDEXCEPT.

Figure 2. The level of the pancreatic neck transection of the two groups. The green dotted line illustrates the level of the pancreatic neck transection. (a). illustrates the level of the pancreatic neck transection of Conventional transection group, in which surgeons will transect the pancreatic neck above the mesenteric-portal axis. (b). illustrates the level of the pancreatic neck transection of Extended transection group, in which surgeons will transect the pancreatic neck at more than 5 mm and less than 10 mm beyond the left side of the mesenteric-portal axis.

Authors' contributions

Bing Peng obtained funding for this study. Yunqiang Cai proposed the conceptualization. Jiaying You, Jing Zhang, Xin Wang and He Cai designed the study. Hongjian Wang calculated the sample size. Bing Peng, Yunqiang Cai, Yongbin Li, Chao Yu, Lei Wang, and Xu Zhou performed the operations. Jiaying You and Jing Zhang drafted the manuscript. Yunqiang Cai and Bing Peng contributed to critical revision of the manuscript and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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Competing Interests statement

None declared.

Acknowledgements

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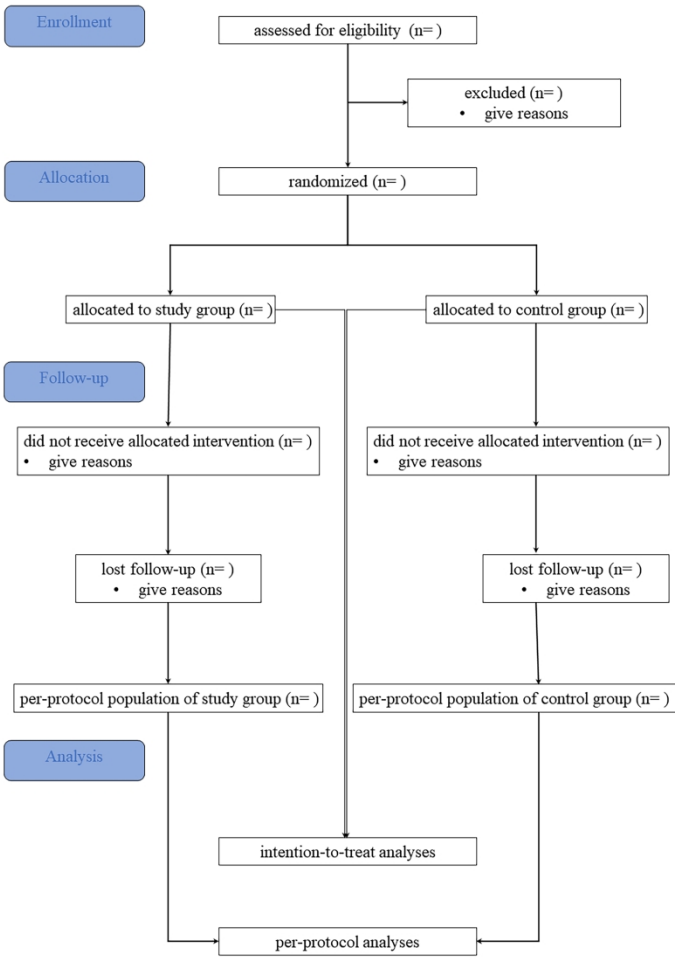

Figure 1. Flow diagram for LPDEXCEPT.

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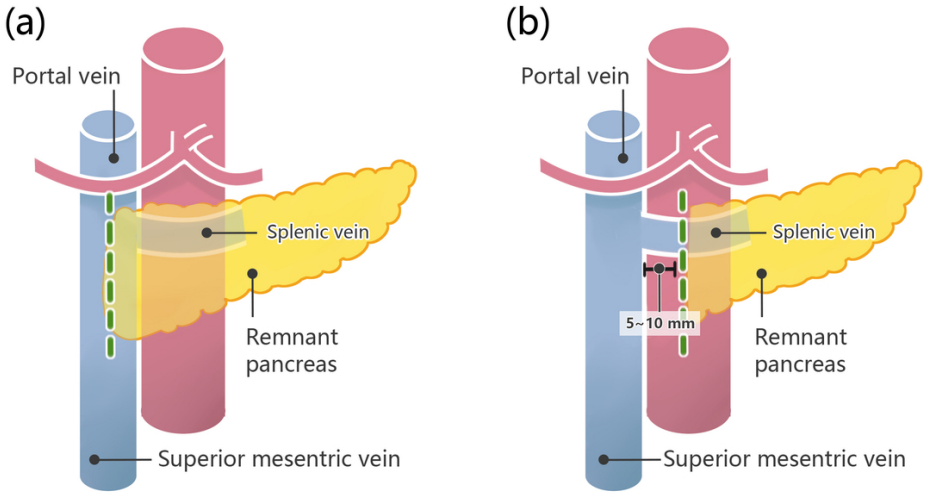

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98x56mm (300 x 300 DPI)

Table 1: Participant timeline and data collection for LPDEXCEPT

	Study period					
Time point / Items	preoperative eligibility assessment	allocation	intraoperatively	Before discharge postoperatively	Follow-up	Close-out
					1st month postoperatively	3rd month postoperatively
Patient demographics	✓					
Informed consent	✓					
Blood routine	✓			✓		
Coagulation routine	✓					
Blood biochemistry	✓			✓		
Enhanced CT scan	✓			✓		
Allocation record		✓				
Surgical videos			✓			
Surgical record			✓			
Postoperative records				✓	✓	✓
Histopathological findings				✓	✓	
Other therapy (if necessary)				✓	✓	✓

Patient demographics includes date of admission, year of birth, sex, body mass index, previous surgical history, preoperative biliary drainage, Nutrition risk score, WHO-ECOG score, location of the tumor, diameter of the tumor, diameter of the main pancreatic duct, and history of neoadjuvant therapy.

Surgical record includes date of operation, ASA scores, location of the pancreatic neck transection (extended or conventional pancreatic neck transection), pancreatic texture, diameter of the main pancreatic duct, duration of pancreaticojejunostomy anastomosis, duration of the operation, estimated blood loss, whether to convert to open surgery or other procedures, whether to preserve the pylorus, and whether to resect and reconstruct the main veins.

Postoperative records include blood transfusion, date of soft solid diet, date of drain removal, date of nasogastric tube removal, drain and production amylase, date of discharge, type of complication, reoperation and Clavien-Dindo grade, cost for hospitalization.

Histopathological findings include location of the tumor, size of the tumor, histological type, surgical margin status, and the T&N classification and American Joint Committee on Cancer staging (AJCC) for malignant tumors.

Other therapy includes readmission, treatment for any surgical complications, adjuvant therapy for malignant tumors, and the cost for readmission.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page No.
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	14
	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	14
	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)	-
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	-
Objectives	7	Specific objectives or hypotheses	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	6
	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)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
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	6
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	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	8

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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
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	8，9
	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	8，9
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	8，9
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	10，11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10，11
	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)	10，11
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	9

	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	9
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	10
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	-
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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
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	-

Informed Consent for Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): a multicenter superiority randomized controlled trial

Informed page

Dear Mrs. /Mr.,

Thank you for your interest in our clinical research! We will invite you to participate in a randomized controlled clinical trial of extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT).

Before you decide whether to participate in this study, please read the following as much as possible to help you understand the research, the purpose, the research process, and deadlines, and what may be brought after you participate in this study, which might be benefits, risks or discomfort. If you prefer, you can also discuss it with your family, friends, or ask your doctor for an explanation.

This clinical trial has been approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2023-167) in March 2023. And the number of participants in this study is expected to be 154.

I. Why to participate in this trial? (Research background and research purposes)

Pancreaticoduodenectomy is the standard procedure for patients with malignant or benign tumors of the pancreatic head, the lower common bile duct, and the periampullary area of the duodenum. Since Gagner and his colleagues performed and introduced the first total laparoscopic pancreaticoduodenectomy (LPD) in 1994, LPD has become progressively acknowledged for its advantages such as less bleeding, less pain, and faster recovery.

Despite the advances in laparoscopic technology, postoperative pancreatic fistula (POPF) remains one of the most severe complications of LPD, which occurs in around 20% of patients. POPF is typically associated with secondary complications, such as post-pancreatectomy hemorrhage, intra-abdominal infection. These could lead to prolonged length of hospital stay, increased hospital cost, and even death. Therefore, prevention of POPF has always been of high priority in pancreatic surgery.

The level of pancreatic neck transection during LPD is not conclusive. Theoretically, the level of pancreatic transection can significantly affect the occurrence of POPF by influencing both the blood supply to the anastomosis and the location of the main pancreatic duct in the pancreatic transverse section. The head of the pancreas is supplied by the anterior and posterior pancreaticoduodenal arterial arcades which are formed by branches from the celiac trunk and the superior mesenteric artery. The body and tail of the pancreas are supplied by branches from the splenic artery. And there is an intermediate zone lacking proper vascularization in the neck of the pancreas, called “vascular watershed”. Therefore, the level of pancreatic neck transection might influence the pancreatic stump vascularization. Strasberg and his colleagues have studied the impact of the defects of pancreatic stump vascularization on POPF and showed there is a statistically significant correlation. The main pancreatic duct arises in the tail of the pancreas, and lies midway between the superior and inferior margins and slightly more posterior than anterior through the tail and body of the pancreas. Then it

turns caudad and posterior on reaching the head of the pancreas. Therefore, the level of pancreatic neck transection could influence the location of the main pancreatic duct in the pancreatic transverse section. Angzhi Li and his colleagues have studied the impact of the location of the pancreatic duct on POPF. And they found the risk of POPF was reduced when the center of pancreatic duct is far from the edge of pancreas.

Bardol and his colleagues conducted a retrospective cohort study and consolidated that a long remnant pancreatic neck could be an independent risk factor for POPF after pancreaticoduodenectomy. However, to date, there exists no randomized study dedicated to answering whether patients could benefit from extended pancreatic neck transection during LPD. Thus, we conduct a multicenter randomized trial, LPDEXCEPT, with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

The broad goal of this trial is to evaluate the superiority of extended pancreatic neck transection during LPD.

II. What will be done if you participate in the research?

If you meet the inclusion criteria and agree to participate, you will be tested according to the following steps: divided into two groups according to the study plan, respectively, undergoing extended pancreatic neck transection or conventional pancreatic neck transection during LPD. You may be assigned in any group. All patients underwent routine nursing of biliary and pancreatic surgery, and collected various indexes before, during and after surgery. At the same time, follow-up for 3 months. The time points of follow-up were the first and third month postoperatively. The follow-up method was ward follow-up combined with telephone follow-up.

III. What are the alternative treatment options?

Patients with resectable benign or malignant tumors of the lower common bile duct, periampullary region of the duodenum, and head of the pancreas could participate in this trial. Alternative treatment options for patients with benign tumors include regular follow-up with conservative observation. According to the existing guidelines, surgical resection is preferred for patients with resectable malignant tumors, and no other treatment alternatives are recommended.

IV. Who can participate in this study? Who is not suitable for research?

Who can:

(1) Patients with benign or resectable malignant tumors of the lower common bile duct, Vater ampulla, head or uncinate process of the pancreas.

(2) 18 years old < age < 80 years old, no gender limit.

(3) Patient is expected survival beyond 3 months.
(4) No pregnancy or pregnancy plan within 3 months after surgery.
(5) Nutrition risk score <3 according to the Nutritional Risk Screening for Inpatients 2002 (NRS2002) standard score.
(6) No contraindication to surgery for anesthetic evaluation.
(7) The subjects voluntarily joined the study and signed an informed consent form, with good compliance and cooperation with follow-up.

Who not:

(1) Patients with borderline resectable and unresectable malignancies.
(2) Patients undergoing neoadjuvant chemotherapy or radiotherapy.
(3) Patients with tumors exceeding the level of the gastroduodenal artery as measured by preoperative radiography.
(4) Intraoperative exploration reveals tumor adhesions with portal vein-superior mesenteric vein, requiring revascularization and reconstruction.
(5) Operation transfers to open.
(6) Operation transfers to other procedure.

V. Adverse reactions, risks, and protective measures for participating in the study.

The main adverse reactions and risks are as follows:

1. In the operation, the surgical method is determined according to medical conditions according to the condition.

2. Due to the patient's condition (critical, complicated, poor systemic conditions), individual differences, sudden and sudden recession may occur during and after surgery, multiple organ failure (such as heart failure, respiratory failure, liver failure, renal function) Failure, DIC, etc.) or unpredictable changes in the condition can be life-threatening.

3. Major bleeding, hemorrhagic shock may occur during surgery, and life-threatening.

4. The operation is due to anatomical variation and severe adhesion for therapeutic purposes. It may be inevitable to damage surrounding and nearby tissues and organs, and the corresponding organs need to be repaired or reconstructed.

5. Special medical supplies such as chemotherapy pumps, anastomotic devices, etc. may be used during surgery, and special treatments such as radiofrequency therapy and cryotherapy may be used during surgery.

6. Tumor patients may not be able to undergo surgical resection due to the condition, or recurrence and metastasis after resection, requiring further treatment.

7. Recurrent bleeding after surgery, local, systemic infection, bile leakage, pancreatic leakage, intestinal leakage, anastomotic leakage, and other changes in the condition may be life-threatening and require reoperation if necessary.

8. Other unforeseen or unpredictable adverse consequences and medical risks.

9. May need to be admitted to the ICU ward, if necessary, after surgery.

10. Postoperative examination may be inconsistent with preoperative diagnosis and intraoperative diagnosis. The final diagnosis is based on postoperative examination.

11. Determine the risk of biopsy of the lesion under the endoscope under the condition of the operation.
12. During the operation, malignant tumor metastasis is found, and it is difficult to cure radically or radically. The risk of radical resection is great. Only palliative anastomosis is possible.
13. During the operation, the abdominal cavity is widely metastasized, and it is impossible to perform resection or palliative anastomosis.
14. Postoperative abdominal adhesions, intestinal adhesions, intestinal obstruction, may require relevant treatment.
15. Long-term bed rest, pulmonary infection, and deep vein thrombosis may occur.
16. Incision healing may occur after surgery, infection of the incision, incision splitting, incisional hernia, etc.
17. Pancreatic exocrine insufficiency.
18. Laparoscopic pancreaticoduodenectomy may be due to tissue adhesion, intraoperative bleeding, etc.
19. Pneum abdominal syndrome, etc.

VI. What will be done in the event of any of these adverse events during the study?

If there is any discomfort in the study, or the condition changes, or any unexpected situation, regardless of whether it is related to treatment, you should promptly notify your doctor, he/she will make an accurate judgment and medical treatment. deal with. If the patients participating in the trial have the above complications, they will form a professional medical team to deal with and treat them for the first time. If an adverse event occurs in a clinical trial, the Medical Expert Committee will determine if it is related to surgery or trial. The treatment and examinations required for other diseases that you have combined at the same time will not be included in the free range.

VII. Possible benefits of participating in the Study.

By participating in this study, your condition may improve. And the study may help determine which treatments are safer and more effective in treating other patients with conditions like yours.

VIII. The relevant costs.

Subjects will not pay for participation in this trial, except for the costs incurred during the treatment.

IX. The confidentiality of clinical data.

Your medical records (research medical records, CRF, test results, etc.) will be kept completely at

the hospital where you are attending. The doctor will record the results of the tests and other tests on your medical record. Researchers, ethics committees, and higher-level medical administrations will be allowed to access your medical records. Any public report about the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. According to medical research ethics, in addition to personal privacy information, experimental data will be available for public inquiry and sharing. Query and sharing will be limited to web-based electronic databases, ensuring that no personal privacy information will be disclosed.

X. Do you have to participate in the trial?

Whether or not to participate in the research is entirely up to you. You may decline to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with the doctor and will not affect your medical or other benefits.
For your best interest, your doctor or researcher may discontinue your participation in this study at any time during your research.

Signature page

Clinical Research Project: Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): a multicenter superiority randomized controlled trial.

Research Center Name:_____

Subject's Statement: I have carefully read the contents of the informed consent form, and the researchers have answered my questions. I fully participated in the study and fully cooperated with the researcher after fully understanding the purpose, method, possible therapeutic benefits and possible risks and other provisions mentioned in the informed consent form. I understand that I can withdraw from the study at any time, and I do not need any reason. The medical services I receive and the legal rights I enjoy are not affected at all. Finally, I decided to agree to participate in this study and to ensure compliance with my doctor's advice.

Subject Signature:_____

Date:_____

Contact Number:_____

Subject's Legal Agent signature (If applicable):

Date:_____

Contact Number:_____

Doctor's Statement: I have explained fully detail to the subjects, including the potential risks.

Doctor Signature:_____

Date:_____

Contact Number:_____

Ethics Committee on Biomedical Research of West China Hospital of Sichuan University
Contact Number:028-85422654，028-85423237

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探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系临床研究知情同意书

尊敬的受试者

我们邀请您参加四川大学华西医院批准开展的“探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系”课题研究。本研究将在贵州医科大学附属医院、攀枝花中心医院、山东省立医院、复旦大学附属肿瘤医院、广东省中医院、乐山市人民医院、云南省第一人民医院、常州市第一人民医院、齐鲁医院、南方医院等医院共同开展，估计将有 184 名受试者自愿参加。本研究已经得到四川大学华西医院生物医学伦理审查委员会的审查和批准。

1. 为什么要开展本项研究？

胰十二指肠切除术是治疗胰腺头部、胆总管下段及十二指肠壶腹周围肿瘤的标准术式。随着微创外科理念的不断发展，腹腔镜胰十二指肠切除术由于具有创伤小、出血量少、恢复快、疼痛轻等优势而得以发展。

胰瘘是 LPD 术后常见的并发症。探究 POPF 发生相关性因素，从而精准预防和管理 POPF、降低 POPF 发生率是胰腺外科领域主要研究内容。

目前导管对黏膜是学界广泛接受的胰肠吻合方式，手术操作时须将胰颈切缘面的主胰管和小肠黏膜进行缝合，既往相关研究表明主胰管在胰颈切缘面的位置是影响手术时吻合操作的因素之一，主胰管是否在切缘中央与术后是否发生 POPF 相关。主胰管在胰腺不同部位的走行位置不同：在胰腺体尾部，主胰管走行于胰腺的中间；从胰腺体部向胰腺头部的过程中，主胰管走行方向逐渐偏向足侧和后侧。因此，LPD 手术过程中，离断胰腺颈部的位置决定了主胰管在胰腺切缘断面的位置。

胰腺各部分动脉血供不同：胰腺头部的血供主要由胃十二指肠动脉发出的胰十二指肠上动脉和肠系膜上动脉发出的胰十二指肠下动脉形成的胰十二指肠前后动脉弓完成；胰腺体尾部的血供主要由脾动脉发出的数支分支完成。胰腺颈部血供由胰背动脉完成，而该动脉常存在变异和缺失，因此胰腺颈部常存在一段乏血供区。因此，在 LPD 术中，离断胰腺颈部的位置也影响胰腺切缘面血供是否充足。

综合上诉两方面原因，LPD 术中离断胰腺颈部的位置在学界存在争议。既往一份回

顾性研究表明，在距离肠系膜上静脉-门静脉左侧缘 7mm 处离断胰腺颈部是 POPF 的保护性因素。但该结论有待进一步前瞻性随机对照试验研究证实。

因此，本研究项目拟通过开展回顾性及前瞻性两部分研究工作探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系。

2. 如果参加研究，您需要做什么？

您首次住院期间除常规诊疗过程外无特殊额外工作。首次手术后 3 月内需按医生要求进行随访。受试期间，您可能随机被分配到对照组和实验组。对照组在 LPD 术中将在门静脉-肠系膜上静脉正前方离断胰腺颈部；实验组 LPD 术中将在门静脉-肠系膜上静脉左侧缘 0.5-1.0cm 处离断胰腺颈部。

3. 可供选择的诊疗方案有哪些？

患者为可切除的胆总管下段、十二指肠壶腹周围、胰腺头部良恶性肿瘤。其中良性肿瘤患者可选择的其他诊疗方法包括：定期随访保守观察治疗。依据现有指南，可切除的恶性肿瘤患者首选手术切除，无其他诊疗方法推荐。

4. 哪些人不宜参加研究？

如果您为 1）临界可切除及不可切除恶性肿瘤患者 2）行新辅助放化疗患者 3）术前影像学判断肿瘤超过胃十二指肠动脉水平患者 4)术中探查发现肿瘤与门静脉-肠系膜上静脉粘连，需行血管切除重建患者 5）术中中转开腹患者 6）术中探查后转行其他手术方式患者，则不宜参加本研究。7）根据《住院患者营养风险筛查 2002（NRS2002）》标准评分，营养风险评分＜3 分。

5. 参加研究有哪些风险？

参加研究，患者将面临行腹腔镜胰十二指肠切除术常规面临的麻醉风险及手术风险，具体包括：

A. 麻醉风险

1）麻醉过程中可能进行以下某一项或多项操作，包括气管插管、椎管内穿刺、周围神经阻滞、深静脉穿刺置管术、动脉穿刺置管术、喉罩插入、气管切开术、气管和支气管镜检查、食管超声波检查、有创血液动力学监测等。这些操作均可能引起组织出血、神经损伤、创伤、感染、坏死等。

2）根据麻醉操作常规，按照《中华人民共和国药典》要求使用各种、各类麻醉药后，病人可能出现中毒、过敏、高敏、神经毒性等反应，导致休克、严重脏器功能损害、呼吸心跳停止，甚至生命危险。已麻醉时，特别是急症和饱腹病人发生胃内容物反流、误吸、喉痉挛、呼吸道梗阻、神经反射性休克和心律失常等而致重要脏器功能损害，危及生命。

3）气管插管可引起牙齿脱落、口唇、舌、咽喉、声带、气管和支气管损伤，喉痉挛、气管痉挛、支气管痉挛及功能损害。气管插管困难通气不能维持时，可能需要进行紧急气管切开术，缺氧时可危及生命。

4）椎管内麻醉及区域麻醉发生神经、血管、脊髓等组织结构损伤，可能出现全脊髓麻醉、截瘫、椎管内感染、血肿、腰痛、头痛、肢体伤残、甚至呼吸心跳停止等危及生命。

5）患者本身合并其他疾病或有重要脏器损害者，相关并发症和麻醉危险性显著增加。

6）麻醉方法的选择和改变由实施麻醉的医师根据病情和手术的需要决定。 7）可能发生术中知晓和术后回忆。

8）其它发生率极低或难以预料的意外和并发症，以及其它不可预料的不良后果。

9）麻醉手术中输血输液可能发生致热源反应、过敏反应、血源性传染病等。

B. 手术风险

1）术中损伤神经、血管及邻近器官，如：脾、胃肠道、肾脏、肾上腺等。

2）术中大出血，导致失血性休克，严重者死亡（脾动/静脉、门静脉损伤）。

3）伤口积液、血肿、感染、裂开、延迟愈合或不愈合，瘘管及窦道形成，切口疝。

4）术后乳糜瘘，需长时间保持引流管通畅或经皮穿刺引流，需长时间药物治疗（生长抑素或生长抑素类似物），症状严重者需介入、手术等侵入性治疗，严重者可能导致死亡。

5）术后胆漏，胆肠吻合口瘘，需行腹腔通畅引流，部分胆痰可自愈，若常规治疗以及引流无效、病情恶化时，需行手术治疗。

6）术后手术部位或腹腔出血，可能需要行介入治疗，必要时再次手术。

7）术后腹腔积液，腹膜炎，腹腔感染，甚至腹腔脓肿，需再次手术可能。

8）术后胰瘘，若出现临床相关胰瘘，不排除二次穿刺甚至再次手术治疗，甚至危及患者生命。

9）术后肠粘连，粘连性肠梗阻。

10）营养性并发症：营养不良、体重减轻、贫血、腹泻和脂肪泻、代谢性骨病。

11）脑并发症：脑血管意外、癫痫。

12）呼吸并发症：肺不张、肺感染、胸腔积液、气胸等。

13）心脏并发症；心律失常、心肌梗死、心衰、心跳骤停。

14）血栓性静脉炎，以致肺栓塞、脑栓塞或其他部位栓塞。

15）多脏器功能衰竭（包括弥漫性血管内凝血）。

16）水电解质平衡紊乱。

17）诱发原有疾病恶化。

18）术中胃肠道损伤，导致术后胃肠漏，胃肠吻合口瘘可能。

19）术后胃排空障碍，出现术后腹胀、恶心、呕吐。

20）术后门静脉系统、肠系膜血管血栓形成。

21）胰性脑病。

22）术后成人呼吸窘迫综合症（ ARDS ）。

23）术后胰腺外分泌功能不全，导致血糖升高、甚至糖尿病可能。

24）术后胰腺内分泌功能不全，导致消化吸收功能障碍，导致顽固性腹泻等。

25）术后胰源性门静脉高压症，导致消化道大出血等。

26）术后胰源性胸水和腹水。

27）若为恶性肿瘤，肿瘤切除术后复发，远处转移。

28）术后胃肠道出血，应激性溃疡，严重者死亡。

29）如果卧床时间较长可能导致肺部感染，泌尿系统感染，褥疮，深静脉血栓及肺栓塞、脑栓塞等。

30）术后远期并发症：胆肠吻合术后可发生胆肠吻合口狭窄、胆管结石、胆管炎、肝脓肿；胃部分切除及胃肠吻合术后可能导致营养不良、吻合口溃疡、消化道出血、倾倒综合征；胰腺切除及胰肠吻合术后可能导致胰腺内分泌及外分泌功能不全、胰肠吻合口狭窄、慢性胰腺炎、胰管结石。

31）术后诊断可能与术中冰冻检查结果不一致，最终诊断根据术后病理结果决定。

32）其它目前无法预料的风险和并发症。

6. 研究过程中受试者出现上述不良事件时，将如何处理？

若发生不良事件应及时由医生或患者报告给研究者，研究者在病例报告表的相应位置做详细记录，研究者应在尊重患者意愿及选择的前提下协助患者积极处理不良事件，争取获得最佳的预后。同时对可能发生的不良事件进行预防。若发生严重不良事件时，研究者及医护人员将按照严重不良事件救治预案进行处理：报告：研究者向科室负责人及医院值班人员报告不良事件性质，并在 24 小时内报告伦理委员会及相关主管部门。及时救治受试者：一旦发生严重不良事件，根据受试者具体不良事件情况迅速采取相应诊疗措施，对受试者进行抢救，必要时送 ICU 诊治。记录：研究者在原始病案和 CRF 表中记录受试者的症状、体征、实验室检查，严重不良事件出现时间、持续时间、程度、处理措施和经过，保证记录完整、真实、准确、及时。填写严重不良事件报告表。随访：研究者对受试者不良事件进行随访，根据病情决定随访时间，在随访过程中给予必要的处理及治疗措施，确保将受试者损害降至最低，充分保证受试者安全。并且详细记录随访经过和处理结果。当发生严重不良事件时，研究将对受试者进行及时救治，并依据相关法律法规给予适当补偿。

7. 参加研究有哪些可能的好处？

参加本项研究，您的病情有可能获得改善，本项研究还有助于确定哪种治疗方法可以更安全有效地治疗与您具有相似病情的其他病人。

8. 参加研究需要支付有关费用吗？

研究员将应当公平、合理地选择受试者。除需要支付诊疗过程中产生的费用外，受试者参加本研究不支付其他任何费用。

9. 个人信息是保密的吗？

您的研究资料将保存在四川大学华西医院，研究者、研究主管部门、伦理审查委员会可查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私和个人信息。

10. 我必须参加研究吗？

参加本项研究是完全自愿的，您可以拒绝参加研究，或在试验的任何阶段随时退出本研究而不会受到歧视和报复，其医疗待遇与权益不受影响。如果您决定退出本研究，请与您的医生联系，以便妥善诊疗疾病。

受试者声明：我已经阅读了上述有关本研究的介绍，我的研究人员已向我充分解释和说明了本研究的目的、操作过程以及参加本研究可能存在的风险和潜在的获益，并回答了我所有相关问题。自愿参加本研究。

我同意☐ 或拒绝☐ 除本研究以外的其他研究利用我的研究资料和生物标本。

受试者正楷姓名：_____

受试者签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

受试者的联系电话：_____ 手机号：_____

法定代理人正楷姓名：_____ （如适用）

与受试者关系：_____

法定代理人签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

需法定代理人签署的原因：_____

见证人正楷姓名：_____ （如适用）

见证人签名：_____ 日期：__ __ __ 年 __ __ 月 __ __ 日

需见证人签署的原因：_____

医生声明：我已对上述参加本研究的自愿者说明了该项研究的有关细节，并且为他/她提供一份签署过的知情同意书的原件。我确认已向受试者详细解释了本研究的情况，特别是参加本研究可能产生的风险与受益、免费与补偿、损害与赔偿、自愿与保密等伦理原则和要求。

医生签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

医生的联系电话：_____

四川大学华西医院生物医学伦理审查委员会 联系电话：028-85422654，028-85423237

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Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial

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- **Title:**

Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): protocol for a multicenter superiority randomised controlled trial.

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- **Structured abstract:**

Introduction: Postoperative pancreatic fistula (POPF) remains one of the most severe complications of laparoscopic pancreaticoduodenectomy (LPD). Theoretically, transecting the pancreatic neck more distally has both advantages (more blood supply, and more central pancreatic duct) and disadvantages (maybe

smaller the pancreatic duct) in preventing POPF. This theoretical contradiction pushed us to organize this trial to explore the impact of the level of pancreatic transection in clinical practice. We conduct this randomised trial with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

Methods and analysis: The LPDEXCEPT trial is a multicenter, randomized-controlled, open-label, superiority trial in 4 centers whose annual surgical volume for LPD is more than 25 cases with pancreatic surgeons who had completed their learning curve. A total of 154 patients who meet the inclusive and exclusive criteria are randomly allocated to the extended pancreatic neck transection group or conventional pancreatic neck transection group in a 1:1 ratio. The stratified randomised block design will be applied, with stratified factors are surgical center and the diameter of the main pancreatic duct measured by preoperative CT scan (preMPD). The primary outcome is the incidence of the clinically relevant pancreatic fistula.

Ethics and dissemination: Ethics Committee on Biomedical Research of West China Hospital of Sichuan University has approved this trial in March 2023(Approval No.2023-167). Results of this trial will be published in peer-reviewed journals and conference proceedings.

Registration details: ClinicalTrials.gov: NCT05808894

• Strengths and limitations of this study

1. This study was designed as a multicenter, randomised, controlled, open-label, superiority trial with two parallel groups, and had been registered internationally.

2. The patients in the study group obtain extended pancreatic neck transection during LPD, transecting the pancreatic neck at more than 5 mm and less than 10 mm beyond the left side of the portal vein. And the patients in the control group obtain conventional pancreatic neck transection, transecting the pancreatic neck above the mesenteric-portal axis.

3. This study applied stratified randomised block design, whose stratified factors

are surgical center and the diameter of the main pancreatic duct measured by the preoperative abdominal CT scan. This will balance possible bias among research centers and pancreatic features.

4. The main limitation is that this study is carried out by a large team of researchers, including surgeons, radiologists, pathologists, data collectors, and statisticians. The coordination of this team is a big challenge.

5. LPDEXCEPT is an open-label trail, however, the primary and secondary outcomes are objective conditions which cannot be influenced by researchers.

• Introduction

Pancreaticoduodenectomy is the standard procedure for patients with malignant or benign tumors of the pancreatic head, the lower common bile duct, and the periampullary area of the duodenum. Since Gagner and his colleagues performed and introduced the first total laparoscopic pancreaticoduodenectomy (LPD) in 1994[1], LPD has become progressively acknowledged for its advantages such as less bleeding, less pain, and faster recovery [2-4].

Despite the advances in laparoscopic technology, postoperative pancreatic fistula (POPF) remains one of the most severe complications of LPD, which occurs in around 20% of patients [4,5]. POPF is typically associated with secondary complications, such as post-pancreatectomy hemorrhage, intra-abdominal infection. These could lead to prolonged length of hospital stay, increased hospital cost, and even death [6,7]. Therefore, prevention of POPF has always been of high priority in pancreatic surgery.

Theoretically, the level of pancreatic transection can significantly affect the occurrence of POPF by influencing both the blood supply to the anastomosis and the location of the main pancreatic duct in the pancreatic transverse section, and maybe also the size of pancreatic duct. The head of the pancreas is supplied by the anterior and posterior pancreaticoduodenal arterial arcades which are formed by branches from the celiac trunk and the superior mesenteric artery. The body and tail of the pancreas are supplied by branches from the splenic artery [8]. And there is an intermediate zone lacking

proper vascularization in the neck of the pancreas, called "vascular watershed" [8]. Therefore, the level of pancreatic neck transection might influence the pancreatic stump vascularization. Strasberg et al. have studied the impact of the defects of pancreatic stump vascularization on POPF and showed there is a statistically significant correlation [9,10]. The main pancreatic duct arises in the tail of the pancreas, and lies midway between the superior and inferior margins and slightly more posterior than anterior through the tail and body of the pancreas. Then it turns caudad and posterior on reaching the head of the pancreas [8]. Therefore, the level of pancreatic neck transection could influence the location of the main pancreatic duct in the pancreatic transverse section. Several studies had revealed the association between the location of the pancreatic duct and POPF [11,12]. And they found the risk of POPF was reduced when the center of pancreatic duct is far from the edge of pancreas. And the more distally the surgeon transect the pancreas, the smaller pancreatic duct he (or she) would get. As the small size of the pancreatic duct is the major risk factor for POPF, transecting the pancreatic neck more distally maybe has disadvantages in preventing POPF.

Bardol et al. conducted a retrospective cohort study and consolidated that long remnant pancreatic neck could be an independent risk factor for POPF after pancreaticoduodenectomy [13]. However, to date, there exists no randomised trial dedicated to answering whether patients could benefit from extended pancreatic neck transection. The above theoretical contradiction pushed us to organize a trial to explore the impact of the level of pancreatic transection in clinical practice. Thus, we conduct this multicenter randomised trial, LPDEXCEPT, with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

• Methods and analysis

We wrote this protocol in line with the Standard Protocol Item Recommendation for Interventional Trials (SPIRIT) 2013 guideline [14].

Design

The LPDEXCEPT trial was designed as a multicenter, randomised, controlled, open-label, superiority trial with two parallel groups. The broad goal of this trial is to evaluate the superiority of extended pancreatic neck transection during LPD. The flow diagram for LPDEXCEPT was shown as figure 1.

Patients and public involvement

Neither patients nor the public are involved in design, recruitment, or conduct of this study.

Study population

All patients with an indication for elective LPD will be evaluated. The reasons for laparoscopic approach is the only choice for this trial but not open or robotic are as follows: There are many aspects that differ between open and minimally invasive (laparoscopic and robotic) pancreaticoduodenectomy, including some of the postoperative complications, duration of surgery, intraoperative bleeding, length of hospitalization, and so on [15-18]. And it is still up for debate to choose the approach. Studies would inevitably introduce additional confounding factors once multiple approaches are included. The process of study design and study implementation would also become more complex to eliminate the bias introduced by these confounding factors. In order to control for these biases more simply and to obtain more accurate and trustworthy results, also because laparoscopic surgery is practiced more in our research team, we chose only laparoscopic surgery for this trial. The inclusion and exclusion criteria for patients are as follows:

Participants inclusion criteria

(1) Patients with benign or resectable malignant tumors of the lower common bile duct, Vater ampulla, head or uncinate process of the pancreas.

(2) 18 years old < age < 80 years old, no gender limit.

(3) Patient is expected survival beyond 3 months.

(4) No pregnancy or pregnancy plan within 3 months after surgery.

(5) Nutrition risk score <3 according to the Nutritional Risk Screening for Inpatients 2002 (NRS2002) standard score [19].

(6) No contraindication to surgery for anesthetic evaluation.

(7) The subjects voluntarily joined the study and signed an informed consent form, with good compliance and cooperation with follow-up.

Participants exclusion criteria

(1) Patients with borderline resectable and unresectable malignancies according to the National Comprehensive Cancer Network (NCCN) and the General Office of National Health Commission clinical practice guidelines [20,21].

(2) Patients undergoing neoadjuvant chemotherapy or radiotherapy, because these patients routinely undergo open surgery in our research team.

(3) Patients with tumors exceeding the level of the gastroduodenal artery as measured by preoperative radiography.

(4) Intraoperative exploration reveals tumor adhesions with portal vein-superior mesenteric vein, requiring revascularization and reconstruction.

(5) Operation transfers to open.

(6) Operation transfers to other procedure.

(7) The duct-to-mucosa pancreaticojejunostomy is not performed due to the main pancreatic duct cannot be found intraoperatively.

Interventions

Study group: Extended transection group

The patients in extended transection group obtain extended pancreatic neck transection during LPD. Surgeons will transect the pancreatic neck at more than 5 mm and less than 10 mm beyond the left side of the portal vein.

Control group: Conventional transection group

The patients in conventional transection group obtain conventional pancreatic neck transection during LPD. Surgeons will transect the pancreatic neck above the mesenteric-portal axis.

Figure 2 illustrates the level of the pancreatic neck transection of the two groups.

Outcomes

Primary outcome measures

The primary outcome is the incidence of the CR-POPF according to the International Study Group of Pancreatic Surgery's (ISGPS) definition and grading [22].

Secondary Outcome Measures

The secondary objective of this trial is to compare the incidence of postoperative morbidity (Clavien-Dindo score ≥3), the location of pancreatic duct, the surgical performance of pancreatojejunostomy, and the short-term and long-term pancreatic endocrine and exocrine function between the two groups. Thus, the secondary outcomes include the location of the pancreatic duct in the pancreatic transverse section, the duration of pancreaticojejunostomy, postoperative morbidity, mortality within 3 months postoperatively, and the pancreatic endocrine and exocrine function of the participants at the third month postoperatively and at the first year postoperatively. The location of the pancreatic duct in the pancreatic transverse section will be measured by the way described as following: Before performing the pancreaticojejunostomy, place the pancreatic transverse section in the central position of the lens. Measure the anterior-posterior diameter of the pancreas and the distance of the pancreatic duct from the back of the pancreas. The location of the pancreatic duct in the pancreatic transverse section is equal to the ratio of the distance of the pancreatic duct from the back of the pancreas to the anterior-posterior diameter of the pancreas. Postoperative morbidity will be classified according to the Clavien-Dindo score [23]. For endocrine function, we detect diabetes mellitus development, and the diagnosis and classification of diabetes mellitus is according to the international criteria of diabetes [24]. For pancreatic exocrine function, we defined pancreatic exocrine insufficiency as that stool evacuation was >3 times/day, and pasty or greasy stool was noted, associated with patient's weight loss, and there was a need for enzyme supplementation resulting in recovery of bowel movements and cessation of steatorrhea [25], considering that not all research centers can measure fecal elastase, N-benzol-L-tyrosyl-p-aminobenzoic acid (BT-PABA), or fecal chymotrypsin.

Participating surgeons and hospital criteria

The trials will be conducted in tertiary care hospitals and academic hospitals.

Participating hospitals must be high-volume medical center whose annual surgical volume for LPD is more than 25 cases, according to the consensus on LPD [26]. Participating surgeons must have completed their learning curve for LPD. We defined that a surgeon who had performed more than 104 cases of laparoscopic pancreaticoduodenectomy is considered to have passed the learning curve, according to the study about practice patterns of laparoscopic pancreaticoduodenectomy conducted by Wang et al [27].

Surgical technique details

All study centers will perform the LPD using the optimization of operative procedure. The specific operating procedures and details are reported in our previous articles [28]. In this study, the surgical operation required attention to the following operational details: Firstly, mark the level of the transection on the surface of the pancreas according to the group of participants before transecting the pancreatic neck, and after dissecting the upper and lower margins of the pancreas and revealing the superior mesenteric vein and portal vein. The level of transection in extended transection group is at more than 5 mm and less than 10 mm beyond the left side of the portal vein, while it in the conventional transection group is at the mesenteric-portal axis. Secondly, make sure not to pull on the pancreas and surrounding tissue, and make sure the pancreas is in situ when marking. Thirdly, mark the pancreas from the superior margin to the inferior margin completely with an electrocoagulation hook, and transect the pancreas along the mark to prevent deviation.

Sample size

The sample size was determined based on the primary objective of comparing the incidence of CR-POPF between the two groups. According to the retrospective study[13], extended pancreatic neck transection (≥+7mm) was associated with a lower incidence of CR-POPF than conventional pancreatic neck transection (15.4% vs. 33.3%). Considering this study is a superiority trial, using the one-sided test with 80% power (1-β) at a significance level of 5% (α), the minimal sample size needed to detect

a significant difference is calculated to be 70 patients in each group. Considering the loss of follow-up and washout, we enlarged the sample size by 10%. Then, there are 77 patients in each group, and the final sample size is 154 patients.

Participant timeline.

The trial time schedule of enrolment is estimated to be a 3-year period, followed by a 1-year follow-up visit after discharge from the hospital. Once the eligibility of the patients is confirmed, randomization will be applied. The intervention will be applied intraoperatively. The assessment and visits for patients will be mandatory in the first month, third month, and first year with either telephone or in-hospital follow-up. The participant timeline was shown in the Table 1.

Table 1: Participant timeline and data collection for LPDEXCEPT

	Study period						
Time point / Items	preoperative eligibility assessment	allocation	intraoperatively	Before discharge postoperatively	Follow-up		Close-out
					1st month postoperatively	3rd month postoperatively	1st year postoperatively
Patient demographics	✓						
Informed consent	✓						
Blood routine	✓			✓			
Coagulation routine	✓						
Blood biochemistry	✓			✓			
Enhanced CT scan	✓			✓			
Allocation record		✓					
Surgical videos			✓				
Surgical record			✓				
Postoperative records				✓	✓	✓	✓
Histopathological findings				✓	✓		
Other therapy (if necessary)				✓	✓	✓	✓

Patient demographics includes date of admission, year of birth, sex, body mass index, previous surgical history, preoperative biliary drainage, Nutrition risk score, WHO-ECOG score, location of the tumor, diameter of the tumor, diameter of the main pancreatic duct, history of neoadjuvant therapy, and pancreatic thickness.

Surgical record includes date of operation, ASA scores, location of the pancreatic neck transection (extended or conventional pancreatic neck transection), pancreatic texture, diameter of the main pancreatic duct, duration of pancreaticojejunostomy anastomosis, duration of the operation, estimated blood loss, whether to convert to open surgery or other procedures, whether to preserve the pylorus, whether to resect and reconstruct the main veins, and variation of vessels.

Postoperative records include blood transfusion, date of soft solid diet, date of drain removal, date of nasogastric tube removal, drain and production amylase, date of discharge, type of complication, reoperation and Clavien-Dindo grade, cost for hospitalization, and short-term and long-term pancreatic exocrine and endocrine function.

Histopathological findings include location of the tumor, size of the tumor, histological type, surgical margin status, and the T&N classification and American Joint Committee on Cancer staging (AJCC) for malignant tumors.

Other therapy includes readmission, treatment for any surgical complications, adjuvant therapy for malignant tumors, and the cost for readmission.

Recruitment

The recruiters in each center will screen eligible patients through the outpatient department or inpatient department. The duration of the recruitment period is estimated to be a 36-month interval depending on each center's recruiting rate. No financial incentives will be provided to trial investigators or patients for enrolment in the recruitment period.

Randomization and allocation.

Stratified randomised block design with a block number of four will be applied. The stratified factors are surgical center and the diameter of the main pancreatic duct measured by the preoperative abdominal CT scan (preMPD). Due to pancreatic duct diameter is the main risk factor for pancreatic fistula [29], we included pancreatic duct diameter as a stratification factor. Also, because of the differences in healthcare delivery and quality, the study center was included as another stratification factor, which could allow extrapolability of the study results to other hospitals. According to classification made by the ISGPS [29], the patients will be stratified into preMPD $\leq$ 3 mm and preMPD $>$ 3 mm. Although pancreatic texture is also another major risk factor for pancreatic fistula, this study did not set it as a stratified factor for the following reasons: firstly, although there have been a few studies that have attempted to use CT values to represent pancreatic texture, there is a lack of a more recognized method to accurately assess pancreatic texture preoperatively [30,31]. Secondly, pancreatic texture is not only determined by the type of pathologic diagnosis, but is also influenced by the site of the tumor, size of the tumor, and so on. Besides, it is also difficult to accurately determine the pathologic diagnosis preoperatively, especially to differentiate the CT manifestations of chronic mass pancreatitis and pancreatic adenocarcinoma, both of whose pancreatic texture is firm. Thirdly, too many stratification factors can add to the difficulties in the implementation of the study. Thus, we did not consider the pancreatic texture or pathologic diagnosis as the stratification factor.

A data manager generated the randomization lists by computer system. The randomization lists will not be available to surgeons, recruiters, and data collectors. And the randomization lists will be embedded in a password-protected mobile application which was created to collect and manage data by our study team. The randomization will be centralised through the mobile application. Allocation of each patient will be announced to the surgeon by the mobile application only after the assessment of baseline information of the patients and the upload of the signed informed consent.

Blinding

The patients, surgeons, data collectors, outcome assessors and data analysts are unblinded. The primary outcome of this study is the incidence of CR-POPF. The definition and the criteria of CR-POPF are objective condition and would not be influenced by the patients and surgeons even if they are unblinded. And the data collectors, outcomes assessors and the data analysts are not involved in perioperative management of the patients. Thus, they have no determination of the CR-POPF.

Data collection and management

Baseline characteristics will be recorded before randomization. Intraoperative information, histopathological information, primary outcome, and secondary outcomes will be collected after randomization from hospitalization up to 1 year postoperatively. The detailed data list was shown in the Table 1.

We have created a special mobile application to collect and manage study data. The mobile application and database are password-protect. The investigators and data collectors are to be qualified to the access the mobile application and the database. Data collection will be completed in accordance with standard specification processes. The investigators and data collectors enter the original data into the mobile application.

Data monitoring

Data Monitoring Committee (DMC) has been established. It is not competing interests. Through the combination of our internet-based and instantaneous mobile application, the DMC will conduct data monitoring to ensure that the reported clinical study data

are accurate, complete, and verifiable from source documents throughout the whole trial. An interim analysis is performed on the primary endpoint when 50% of patients have been randomised and have completed the 3 months follow-up. The interim analysis is performed by an independent statistician. The statistician will report to the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The ethics committee decides on the continuation of the trial.

Harms

An adverse event will be defined as any untoward medical occurrence in a subject without regard to the possibility of a causal relationship. All adverse events will be collected and recorded in detail according to the Common Terminology Criteria for Adverse Events (CTCAE V.4.0) after the subject has provided consent and enrolled in the study. And the data will be collected by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University and the ClinicalTrials.gov Protocol Registration and Results System.

Protocol amendments.

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. And the health authorities will be notified in accordance with local regulations.

Auditing.

Auditing will be performed per year, at 50% of the inclusions, and at the end of the study by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The auditing will be independent from investigators.

Confidentiality.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All

databases will be secured with the password-protected data collection system.

Access to data.

All participating investigators will be able to access the data of the registry, perform statistical analysis, discuss the results, and write the scientific manuscripts. Project principal investigators will have direct access to their own site's data sets, and will have access to other sites data by request. Data dispersed to project team members will be blinded of any identifying participant information.

Statistical methods

Statistical analysis will be performed using IBM SPSS statistics Version 25.0 (SPSS Inc., Chicago, IL) and the R programme Version 4.2.1 (R Foundation for Statistical Computing Platform). For continuous variables following a normal distribution, results were reported as the mean ± standard deviation (SD) for the data, otherwise, the median with interquartile range (IQR) was reported. Categorical variables were reported as frequency and percentage. The two-side P value < 0.05 was considered statistically significant. The Chi-Squared test or Fisher's exact test will be used to compare the categorical data between the study group and the control group as appropriate. The independent sample T test will be used to compare the continuous variables following a normal distribution between the two groups. And the continuous non-normally distributed variables will be compared using the Mann-Whitney U test. A Logistic regression analysis will be performed to investigate predictors of CR-POPF. All variables with a p value < 0.1 in a univariable analysis are included in the multivariable Logistic regression analysis.

Bias due to missing data will be investigated by comparing the baseline characteristics of participants with and without missing values. Analysis in all randomly assigned patients (intention-to-treat analysis) will be conducted as sensitivity analyses. In addition, multiple imputations will be used to impute missing data, and the imputed data will also be analyzed as part of the sensitivity analyses. The primary and secondary outcomes will also be analyzed in all eligible patients who began the protocol treatment

(per-protocol population), excluding ineligible patients and those not receiving the allocated treatment from all randomly assigned patients.

• Ethics and dissemination

The ethics approval of the trial has been obtained from the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University in March 2023 (Approval No.2023-167). The ethics Committee of each participating centers had accepted the decision of ethical review of the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University. The English and Chinese versions of the informed consent materials were shown in Appendix 1. Trained research surgeons will introduce the trial to patients who have the indication for LPD. Patients will then be able to have an informed discussion with the participating consultant. Research surgeons will obtain written consent from patients willing to participate in the trial before entering the study.

The result of this study will be reported according to the CONSORT2010 guidelines [32]. Any study results will be published in peer-reviewed journals and conference proceedings. The results will be released to the participating physicians, referring physicians, patients, and the general medical community.

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- **Figure legend**

Figure 1. Flow diagram for LPDEXCEPT.

Figure 2. The level of the pancreatic neck transection of the two groups. The green dotted line illustrates the level of the pancreatic neck transection. (a). illustrates the level of the pancreatic neck transection of Conventional transection group, in which surgeons will transect the pancreatic neck above the mesenteric-portal axis. (b). illustrates the level of the pancreatic neck transection of Extended transection group, in which surgeons will transect the pancreatic neck at more than 5 mm and less than 10 mm beyond the left side of the mesenteric-portal axis.

- **Authors' contributions**

  Bing Peng obtained funding for this study. Yunqiang Cai proposed the conceptualization. Jiaying You, Jing Zhang, Xin Wang and He Cai designed the study. Hongjian Wang calculated the sample size. Bing Peng, Yunqiang Cai, Yongbin Li, Chao Yu, Lei Wang, and Xu Zhou performed the operations. Jiaying You and Jing Zhang drafted the manuscript. Yunqiang Cai and Bing Peng contributed to critical revision of the manuscript and approved the final version of the manuscript. All authors have read and approved the final manuscript.

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- **Competing Interests statement**

  None declared.

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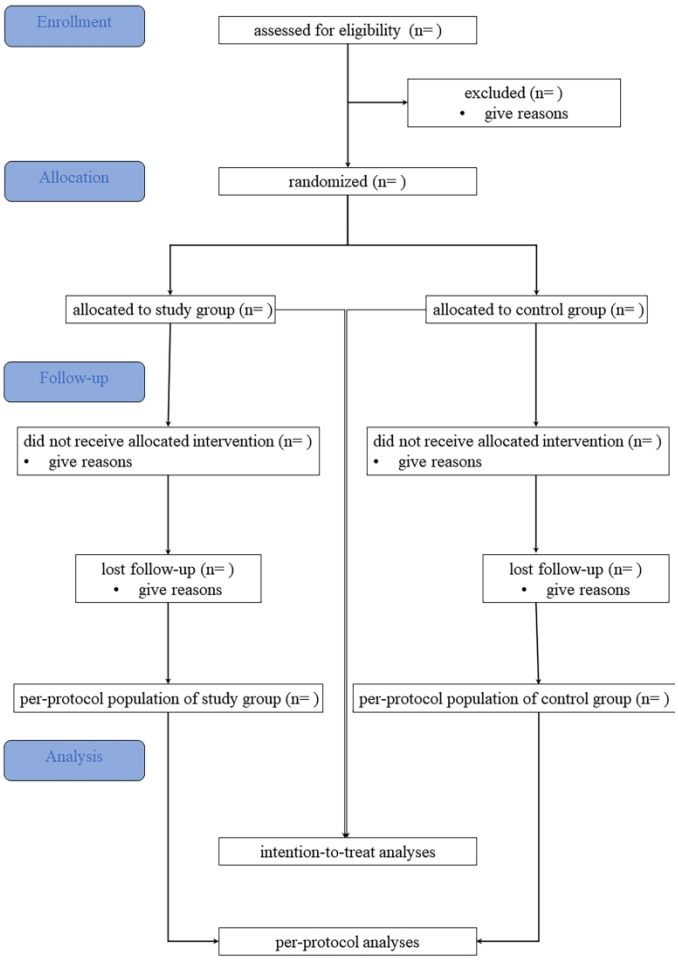

Figure 1. Flow diagram for LPDEXCEPT.

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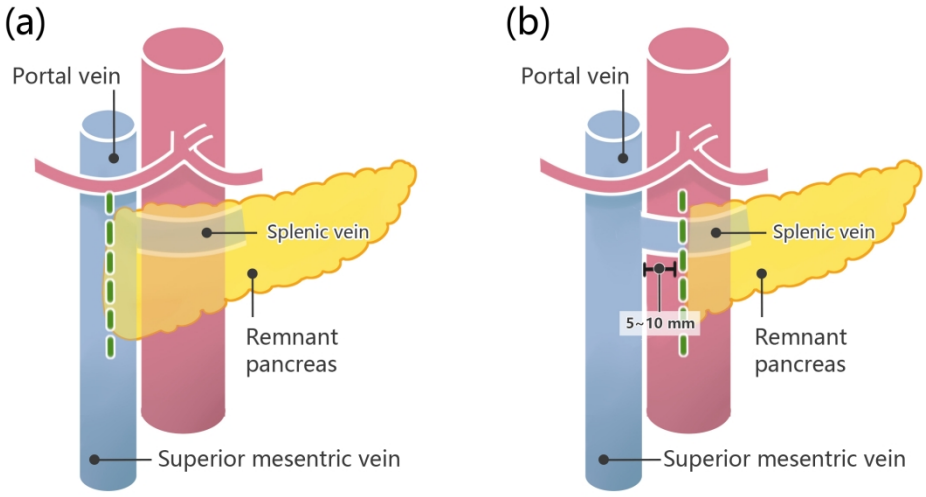

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98x56mm (600 x 600 DPI)

Informed Consent for Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): a multicenter superiority randomized controlled trial

Informed page

Dear Mrs. /Mr.,

Thank you for your interest in our clinical research! We will invite you to participate in a randomized controlled clinical trial of extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT).

Before you decide whether to participate in this study, please read the following as much as possible to help you understand the research, the purpose, the research process, and deadlines, and what may be brought after you participate in this study, which might be benefits, risks or discomfort. If you prefer, you can also discuss it with your family, friends, or ask your doctor for an explanation.

This clinical trial has been approved by the Ethics Committee on Biomedical Research of West China Hospital of Sichuan University (2023-167) in March 2023. And the number of participants in this study is expected to be 154.

I. Why to participate in this trial? (Research background and research purposes)

Pancreaticoduodenectomy is the standard procedure for patients with malignant or benign tumors of the pancreatic head, the lower common bile duct, and the periampullary area of the duodenum. Since Gagner and his colleagues performed and introduced the first total laparoscopic pancreaticoduodenectomy (LPD) in 1994, LPD has become progressively acknowledged for its advantages such as less bleeding, less pain, and faster recovery.

Despite the advances in laparoscopic technology, postoperative pancreatic fistula (POPF) remains one of the most severe complications of LPD, which occurs in around 20% of patients. POPF is typically associated with secondary complications, such as post-pancreatectomy hemorrhage, intra-abdominal infection. These could lead to prolonged length of hospital stay, increased hospital cost, and even death. Therefore, prevention of POPF has always been of high priority in pancreatic surgery.

The level of pancreatic neck transection during LPD is not conclusive. Theoretically, the level of pancreatic transection can significantly affect the occurrence of POPF by influencing both the blood supply to the anastomosis and the location of the main pancreatic duct in the pancreatic transverse section. The head of the pancreas is supplied by the anterior and posterior pancreaticoduodenal arterial arcades which are formed by branches from the celiac trunk and the superior mesenteric artery. The body and tail of the pancreas are supplied by branches from the splenic artery. And there is an intermediate zone lacking proper vascularization in the neck of the pancreas, called “vascular watershed”. Therefore, the level of pancreatic neck transection might influence the pancreatic stump vascularization. Strasberg and his colleagues have studied the impact of the defects of pancreatic stump vascularization on POPF and showed there is a statistically significant correlation. The main pancreatic duct arises in the tail of the pancreas, and lies midway between the superior and inferior margins and slightly more posterior than anterior through the tail and body of the pancreas. Then it

turns caudad and posterior on reaching the head of the pancreas. Therefore, the level of pancreatic neck transection could influence the location of the main pancreatic duct in the pancreatic transverse section. Angzhi Li and his colleagues have studied the impact of the location of the pancreatic duct on POPF. And they found the risk of POPF was reduced when the center of pancreatic duct is far from the edge of pancreas.

Bardol and his colleagues conducted a retrospective cohort study and consolidated that a long remnant pancreatic neck could be an independent risk factor for POPF after pancreaticoduodenectomy. However, to date, there exists no randomized study dedicated to answering whether patients could benefit from extended pancreatic neck transection during LPD. Thus, we conduct a multicenter randomized trial, LPDEXCEPT, with the hypothesis that extended pancreatic neck transection has superiority to conventional pancreatic neck transection.

The broad goal of this trial is to evaluate the superiority of extended pancreatic neck transection during LPD.

II. What will be done if you participate in the research?

If you meet the inclusion criteria and agree to participate, you will be tested according to the following steps: divided into two groups according to the study plan, respectively, undergoing extended pancreatic neck transection or conventional pancreatic neck transection during LPD. You may be assigned in any group. All patients underwent routine nursing of biliary and pancreatic surgery, and collected various indexes before, during and after surgery. At the same time, follow-up for 3 months. The time points of follow-up were the first and third month postoperatively. The follow-up method was ward follow-up combined with telephone follow-up.

III. What are the alternative treatment options?

Patients with resectable benign or malignant tumors of the lower common bile duct, periampullary region of the duodenum, and head of the pancreas could participate in this trial. Alternative treatment options for patients with benign tumors include regular follow-up with conservative observation. According to the existing guidelines, surgical resection is preferred for patients with resectable malignant tumors, and no other treatment alternatives are recommended.

IV. Who can participate in this study? Who is not suitable for research?

Who can:

(1) Patients with benign or resectable malignant tumors of the lower common bile duct, Vater ampulla, head or uncinate process of the pancreas.

(2) 18 years old < age < 80 years old, no gender limit.

(3) Patient is expected survival beyond 3 months.
(4) No pregnancy or pregnancy plan within 3 months after surgery.
(5) Nutrition risk score <3 according to the Nutritional Risk Screening for Inpatients 2002 (NRS2002) standard score.
(6) No contraindication to surgery for anesthetic evaluation.
(7) The subjects voluntarily joined the study and signed an informed consent form, with good compliance and cooperation with follow-up.

Who not:

(1) Patients with borderline resectable and unresectable malignancies.
(2) Patients undergoing neoadjuvant chemotherapy or radiotherapy.
(3) Patients with tumors exceeding the level of the gastroduodenal artery as measured by preoperative radiography.
(4) Intraoperative exploration reveals tumor adhesions with portal vein-superior mesenteric vein, requiring revascularization and reconstruction.
(5) Operation transfers to open.
(6) Operation transfers to other procedure.

V. Adverse reactions, risks, and protective measures for participating in the study.

The main adverse reactions and risks are as follows:

1. In the operation, the surgical method is determined according to medical conditions according to the condition.

2. Due to the patient's condition (critical, complicated, poor systemic conditions), individual differences, sudden and sudden recession may occur during and after surgery, multiple organ failure (such as heart failure, respiratory failure, liver failure, renal function) Failure, DIC, etc.) or unpredictable changes in the condition can be life-threatening.

3. Major bleeding, hemorrhagic shock may occur during surgery, and life-threatening.

4. The operation is due to anatomical variation and severe adhesion for therapeutic purposes. It may be inevitable to damage surrounding and nearby tissues and organs, and the corresponding organs need to be repaired or reconstructed.

5. Special medical supplies such as chemotherapy pumps, anastomotic devices, etc. may be used during surgery, and special treatments such as radiofrequency therapy and cryotherapy may be used during surgery.

6. Tumor patients may not be able to undergo surgical resection due to the condition, or recurrence and metastasis after resection, requiring further treatment.

7. Recurrent bleeding after surgery, local, systemic infection, bile leakage, pancreatic leakage, intestinal leakage, anastomotic leakage, and other changes in the condition may be life-threatening and require reoperation if necessary.

8. Other unforeseen or unpredictable adverse consequences and medical risks.

9. May need to be admitted to the ICU ward, if necessary, after surgery.

10. Postoperative examination may be inconsistent with preoperative diagnosis and intraoperative diagnosis. The final diagnosis is based on postoperative examination.

11. Determine the risk of biopsy of the lesion under the endoscope under the condition of the operation.
12. During the operation, malignant tumor metastasis is found, and it is difficult to cure radically or radically. The risk of radical resection is great. Only palliative anastomosis is possible.
13. During the operation, the abdominal cavity is widely metastasized, and it is impossible to perform resection or palliative anastomosis.
14. Postoperative abdominal adhesions, intestinal adhesions, intestinal obstruction, may require relevant treatment.
15. Long-term bed rest, pulmonary infection, and deep vein thrombosis may occur.
16. Incision healing may occur after surgery, infection of the incision, incision splitting, incisional hernia, etc.
17. Pancreatic exocrine insufficiency.
18. Laparoscopic pancreaticoduodenectomy may be due to tissue adhesion, intraoperative bleeding, etc.
19. Pneum abdominal syndrome, etc.

VI. What will be done in the event of any of these adverse events during the study?

If there is any discomfort in the study, or the condition changes, or any unexpected situation, regardless of whether it is related to treatment, you should promptly notify your doctor, he/she will make an accurate judgment and medical treatment. deal with. If the patients participating in the trial have the above complications, they will form a professional medical team to deal with and treat them for the first time. If an adverse event occurs in a clinical trial, the Medical Expert Committee will determine if it is related to surgery or trial. The treatment and examinations required for other diseases that you have combined at the same time will not be included in the free range.

VII. Possible benefits of participating in the Study.

By participating in this study, your condition may improve. And the study may help determine which treatments are safer and more effective in treating other patients with conditions like yours.

VIII. The relevant costs.

Subjects will not pay for participation in this trial, except for the costs incurred during the treatment.

IX. The confidentiality of clinical data.

Your medical records (research medical records, CRF, test results, etc.) will be kept completely at

the hospital where you are attending. The doctor will record the results of the tests and other tests on your medical record. Researchers, ethics committees, and higher-level medical administrations will be allowed to access your medical records. Any public report about the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. According to medical research ethics, in addition to personal privacy information, experimental data will be available for public inquiry and sharing. Query and sharing will be limited to web-based electronic databases, ensuring that no personal privacy information will be disclosed.

X. Do you have to participate in the trial?

Whether or not to participate in the research is entirely up to you. You may decline to participate in the study or withdraw from the study at any time during the study, which will not affect your relationship with the doctor and will not affect your medical or other benefits.

For your best interest, your doctor or researcher may discontinue your participation in this study at any time during your research.

Signature page

Clinical Research Project: Extended pancreatic neck transection versus conventional pancreatic neck transection during laparoscopic pancreaticoduodenectomy (LPDEXCEPT): a multicenter superiority randomized controlled trial.

Research Center Name:_____

Subject's Statement: I have carefully read the contents of the informed consent form, and the researchers have answered my questions. I fully participated in the study and fully cooperated with the researcher after fully understanding the purpose, method, possible therapeutic benefits and possible risks and other provisions mentioned in the informed consent form. I understand that I can withdraw from the study at any time, and I do not need any reason. The medical services I receive and the legal rights I enjoy are not affected at all. Finally, I decided to agree to participate in this study and to ensure compliance with my doctor's advice.

Subject Signature:_____

Date:_____

Contact Number:_____

Subject's Legal Agent signature (If applicable):

Date:_____

Contact Number:_____

Doctor's Statement: I have explained fully detail to the subjects, including the potential risks.

Doctor Signature:_____

Date:_____

Contact Number:_____

Ethics Committee on Biomedical Research of West China Hospital of Sichuan University
Contact Number:028-85422654，028-85423237

版本号：V2.0 版本日期：2023 年 02 月 21 日

探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系临床研究知情同意书

尊敬的受试者

我们邀请您参加四川大学华西医院批准开展的“探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系”课题研究。本研究将在贵州医科大学附属医院、攀枝花中心医院、山东省立医院、复旦大学附属肿瘤医院、广东省中医院、乐山市人民医院、云南省第一人民医院、常州市第一人民医院、齐鲁医院、南方医院等医院共同开展，估计将有 184 名受试者自愿参加。本研究已经得到四川大学华西医院生物医学伦理审查委员会的审查和批准。

1. 为什么要开展本项研究？

胰十二指肠切除术是治疗胰腺头部、胆总管下段及十二指肠壶腹周围肿瘤的标准术式。随着微创外科理念的不断发展，腹腔镜胰十二指肠切除术由于具有创伤小、出血量少、恢复快、疼痛轻等优势而得以发展。

胰瘘是 LPD 术后常见的并发症。探究 POPF 发生相关性因素，从而精准预防和管理 POPF、降低 POPF 发生率是胰腺外科领域主要研究内容。

目前导管对黏膜是学界广泛接受的胰肠吻合方式，手术操作时须将胰颈切缘面的主胰管和小肠黏膜进行缝合，既往相关研究表明主胰管在胰颈切缘面的位置是影响手术时吻合操作的因素之一，主胰管是否在切缘中央与术后是否发生 POPF 相关。主胰管在胰腺不同部位的走行位置不同：在胰腺体尾部，主胰管走行于胰腺的中间；从胰腺体部向胰腺头部的过程中，主胰管走行方向逐渐偏向足侧和后侧。因此，LPD 手术过程中，离断胰腺颈部的位置决定了主胰管在胰腺切缘断面的位置。

胰腺各部分动脉血供不同：胰腺头部的血供主要由胃十二指肠动脉发出的胰十二指肠上动脉和肠系膜上动脉发出的胰十二指肠下动脉形成的胰十二指肠前后动脉弓完成；胰腺体尾部的血供主要由脾动脉发出的数支分支完成。胰腺颈部血供由胰背动脉完成，而该动脉常存在变异和缺失，因此胰腺颈部常存在一段乏血供区。因此，在 LPD 术中，离断胰腺颈部的位置也影响胰腺切缘面血供是否充足。

综合上诉两方面原因，LPD 术中离断胰腺颈部的位置在学界存在争议。既往一份回

顾性研究表明，在距离肠系膜上静脉-门静脉左侧缘 7mm 处离断胰腺颈部是 POPF 的保护性因素。但该结论有待进一步前瞻性随机对照试验研究证实。

因此，本研究项目拟通过开展回顾性及前瞻性两部分研究工作探究腹腔镜胰十二指肠切除术中胰颈离断位置与术后胰瘘发生的相关性关系。

2. 如果参加研究，您需要做什么？

您首次住院期间除常规诊疗过程外无特殊额外工作。首次手术后 3 月内需按医生要求进行随访。受试期间，您可能随机被分配到对照组和实验组。对照组在 LPD 术中将在门静脉-肠系膜上静脉正前方离断胰腺颈部；实验组 LPD 术中将在门静脉-肠系膜上静脉左侧缘 0.5-1.0cm 处离断胰腺颈部。

3. 可供选择的诊疗方案有哪些？

患者为可切除的胆总管下段、十二指肠壶腹周围、胰腺头部良恶性肿瘤。其中良性肿瘤患者可选择的其他诊疗方法包括：定期随访保守观察治疗。依据现有指南，可切除的恶性肿瘤患者首选手术切除，无其他诊疗方法推荐。

4. 哪些人不宜参加研究？

如果您为 1）临界可切除及不可切除恶性肿瘤患者 2）行新辅助放化疗患者 3）术前影像学判断肿瘤超过胃十二指肠动脉水平患者 4)术中探查发现肿瘤与门静脉-肠系膜上静脉粘连，需行血管切除重建患者 5）术中中转开腹患者 6）术中探查后转行其他手术方式患者，则不宜参加本研究。7）根据《住院患者营养风险筛查 2002（NRS2002）》标准评分，营养风险评分＜3 分。

5. 参加研究有哪些风险？

参加研究，患者将面临行腹腔镜胰十二指肠切除术常规面临的麻醉风险及手术风险，具体包括：

A. 麻醉风险

1）麻醉过程中可能进行以下某一项或多项操作，包括气管插管、椎管内穿刺、周围神经阻滞、深静脉穿刺置管术、动脉穿刺置管术、喉罩插入、气管切开术、气管和支气管镜检查、食管超声波检查、有创血液动力学监测等。这些操作均可能引起组织出血、神经损伤、创伤、感染、坏死等。

2）根据麻醉操作常规，按照《中华人民共和国药典》要求使用各种、各类麻醉药后，病人可能出现中毒、过敏、高敏、神经毒性等反应，导致休克、严重脏器功能损害、呼吸心跳停止，甚至生命危险。已麻醉时，特别是急症和饱腹病人发生胃内容物反流、误吸、喉痉挛、呼吸道梗阻、神经反射性休克和心律失常等而致重要脏器功能损害，危及生命。

3）气管插管可引起牙齿脱落、口唇、舌、咽喉、声带、气管和支气管损伤，喉痉挛、气管痉挛、支气管痉挛及功能损害。气管插管困难通气不能维持时，可能需要进行紧急气管切开术，缺氧时可危及生命。

4）椎管内麻醉及区域麻醉发生神经、血管、脊髓等组织结构损伤，可能出现全脊髓麻醉、截瘫、椎管内感染、血肿、腰痛、头痛、肢体伤残、甚至呼吸心跳停止等危及生命。

5）患者本身合并其他疾病或有重要脏器损害者，相关并发症和麻醉危险性显著增加。

6）麻醉方法的选择和改变由实施麻醉的医师根据病情和手术的需要决定。 7）可能发生术中知晓和术后回忆。

8）其它发生率极低或难以预料的意外和并发症，以及其它不可预料的不良后果。

9）麻醉手术中输血输液可能发生致热源反应、过敏反应、血源性传染病等。

B. 手术风险

1）术中损伤神经、血管及邻近器官，如：脾、胃肠道、肾脏、肾上腺等。

2）术中大出血，导致失血性休克，严重者死亡（脾动/静脉、门静脉损伤）。

3）伤口积液、血肿、感染、裂开、延迟愈合或不愈合，瘘管及窦道形成，切口疝。

4）术后乳糜瘘，需长时间保持引流管通畅或经皮穿刺引流，需长时间药物治疗（生长抑素或生长抑素类似物），症状严重者需介入、手术等侵入性治疗，严重者可能导致死亡。

5）术后胆漏，胆肠吻合口瘘，需行腹腔通畅引流，部分胆痰可自愈，若常规治疗以及引流无效、病情恶化时，需行手术治疗。

6）术后手术部位或腹腔出血，可能需要行介入治疗，必要时再次手术。

7）术后腹腔积液，腹膜炎，腹腔感染，甚至腹腔脓肿，需再次手术可能。

8）术后胰瘘，若出现临床相关胰瘘，不排除二次穿刺甚至再次手术治疗，甚至危及患者生命。

9）术后肠粘连，粘连性肠梗阻。

10）营养性并发症：营养不良、体重减轻、贫血、腹泻和脂肪泻、代谢性骨病。

11）脑并发症：脑血管意外、癫痫。

12）呼吸并发症：肺不张、肺感染、胸腔积液、气胸等。

13）心脏并发症；心律失常、心肌梗死、心衰、心跳骤停。

14）血栓性静脉炎，以致肺栓塞、脑栓塞或其他部位栓塞。

15）多脏器功能衰竭（包括弥漫性血管内凝血）。

16）水电解质平衡紊乱。

17）诱发原有疾病恶化。

18）术中胃肠道损伤，导致术后胃肠漏，胃肠吻合口瘘可能。

19）术后胃排空障碍，出现术后腹胀、恶心、呕吐。

20）术后门静脉系统、肠系膜血管血栓形成。

21）胰性脑病。

22）术后成人呼吸窘迫综合症（ ARDS ）。

23）术后胰腺外分泌功能不全，导致血糖升高、甚至糖尿病可能。

24）术后胰腺内分泌功能不全，导致消化吸收功能障碍，导致顽固性腹泻等。

25）术后胰源性门静脉高压症，导致消化道大出血等。

26）术后胰源性胸水和腹水。

27）若为恶性肿瘤，肿瘤切除术后复发，远处转移。

28）术后胃肠道出血，应激性溃疡，严重者死亡。

29）如果卧床时间较长可能导致肺部感染，泌尿系统感染，褥疮，深静脉血栓及肺栓塞、脑栓塞等。

30）术后远期并发症：胆肠吻合术后可发生胆肠吻合口狭窄、胆管结石、胆管炎、肝脓肿；胃部分切除及胃肠吻合术后可能导致营养不良、吻合口溃疡、消化道出血、倾倒综合征；胰腺切除及胰肠吻合术后可能导致胰腺内分泌及外分泌功能不全、胰肠吻合口狭窄、慢性胰腺炎、胰管结石。

31）术后诊断可能与术中冰冻检查结果不一致，最终诊断根据术后病理结果决定。

32）其它目前无法预料的风险和并发症。

6. 研究过程中受试者出现上述不良事件时，将如何处理？

若发生不良事件应及时由医生或患者报告给研究者，研究者在病例报告表的相应位置做详细记录，研究者应在尊重患者意愿及选择的前提下协助患者积极处理不良事件，争取获得最佳的预后。同时对可能发生的不良事件进行预防。若发生严重不良事件时，研究者及医护人员将按照严重不良事件救治预案进行处理：报告：研究者向科室负责人及医院值班人员报告不良事件性质，并在 24 小时内报告伦理委员会及相关主管部门。及时救治受试者：一旦发生严重不良事件，根据受试者具体不良事件情况迅速采取相应诊疗措施，对受试者进行抢救，必要时送 ICU 诊治。记录：研究者在原始病案和 CRF 表中记录受试者的症状、体征、实验室检查，严重不良事件出现时间、持续时间、程度、处理措施和经过，保证记录完整、真实、准确、及时。填写严重不良事件报告表。随访：研究者对受试者不良事件进行随访，根据病情决定随访时间，在随访过程中给予必要的处理及治疗措施，确保将受试者损害降至最低，充分保证受试者安全。并且详细记录随访经过和处理结果。当发生严重不良事件时，研究将对受试者进行及时救治，并依据相关法律法规给予适当补偿。

7. 参加研究有哪些可能的好处？

参加本项研究，您的病情有可能获得改善，本项研究还有助于确定哪种治疗方法可以更安全有效地治疗与您具有相似病情的其他病人。

8. 参加研究需要支付有关费用吗？

研究员将应当公平、合理地选择受试者。除需要支付诊疗过程中产生的费用外，受试者参加本研究不支付其他任何费用。

9. 个人信息是保密的吗？

您的研究资料将保存在四川大学华西医院，研究者、研究主管部门、伦理审查委员会可查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私和个人信息。

10. 我必须参加研究吗？

参加本项研究是完全自愿的，您可以拒绝参加研究，或在试验的任何阶段随时退出本研究而不会受到歧视和报复，其医疗待遇与权益不受影响。如果您决定退出本研究，请与您的医生联系，以便妥善诊疗疾病。

受试者声明：我已经阅读了上述有关本研究的介绍，我的研究人员已向我充分解释和说明了本研究的目的、操作过程以及参加本研究可能存在的风险和潜在的获益，并回答了我所有相关问题。自愿参加本研究。

我同意☐ 或拒绝☐ 除本研究以外的其他研究利用我的研究资料和生物标本。

受试者正楷姓名：_____

受试者签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

受试者的联系电话：_____ 手机号：_____

法定代理人正楷姓名：_____ （如适用）

与受试者关系：_____

法定代理人签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

需法定代理人签署的原因：_____

见证人正楷姓名：_____ （如适用）

见证人签名：_____ 日期：__ __ __ 年 __ __ 月 __ __ 日

需见证人签署的原因：_____

医生声明：我已对上述参加本研究的自愿者说明了该项研究的有关细节，并且为他/她提供一份签署过的知情同意书的原件。我确认已向受试者详细解释了本研究的情况，特别是参加本研究可能产生的风险与受益、免费与补偿、损害与赔偿、自愿与保密等伦理原则和要求。

医生签名：_____ 日期：__ __ __ __ 年 __ __ 月 __ __ 日

医生的联系电话：_____

四川大学华西医院生物医学伦理审查委员会 联系电话：028-85422654，028-85423237

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Page No.
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	19
	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)	-
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	-
Objectives	7	Specific objectives or hypotheses	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)	4,5

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	7,8
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)	5,6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6,8
	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)	6,8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6,8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
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	6,7
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)	9,10
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	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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	11,12

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	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
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	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	10
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	12,13
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	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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)	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	12,13

	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	12,13
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	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
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	13
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
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	-
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	15
	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	Appendix
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	-