Shark Mouth Modified Pancreaticojejunostomy（SMMP） in Pancreaticoduodenectomy Procedure

National Clinical Trial (NCT) Identified Number:

Principal Investigator: Dianrong Xiu

Organization: Department of General Surgery, Peking University Third Hospital

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Shark Mouth Modified Pancreaticojejunostomy（SMMP） in Pancreaticoduodenectomy Procedure
Study Description:	*We established a new digestive reconstruction technique named SMMP, which had theoretical advantages including easier performed; lower tension and less complication. The pancreaticojejunostomy time, post-operation complication, mortality and hospital stay will be documented to study the safety, efficiency and advantage of this new procedure.*
Objectives:	Primary Objective: To evaluate the new procedure (SMMP) Secondary Objectives: To popularize SMMP
Endpoints:	Primary Endpoint: pancreatic fistula Secondary Endpoints: Mortality ; Morbidity ; pancreaticojejunostomy time ; Hospital stay
Study Population:	*120 cases of Chinese Patients diagnosed with pancreatic cancer or other diseases which need pancreaticoduodenectomy; any gender; 18-80 years old*
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	*Department of General Surgery, Peking University Third Hospital*
Description of Study Intervention:	*The remnant of jejunum is closed by continuous suture. The transverse incision is made on the posterior wall of the jejunum (5 centimeters distal to remnant）, which starts at 0.2 centimeter to the mesenteric border and should never exceed the anti-mesenteric border. In case of large pancreas remnant, a longitudinal jejunum incision will be done at anterior part of anastomosis. The posterior part of anastomosis is two layers of intermittent suture, including seromuscular suture layer and full thickness suture layer. The anterior part of anastomosis is a single layer full thickness suture. At last, the seromuscular layer of the proximal jejunum is sutured with the anterior pancreatic capsule to cover the anterior part of anastomosis.*
Study Duration:	*December, 2017 To December, 2019*
Participant Duration:	*3 months*

1.2 SCHEMA

This section should include a diagram that provides a quick "snapshot" of the study and ideally be limited to 1 page. Below are examples of schematics that show the level of detail needed to convey an overview of the study design. Depending on the nature of your study, one example may be more appropriate than another. Regardless, the examples included here are intended to guide the development of a schematic that is appropriate to the planned study design and will need to be customized for the protocol. Revise with study-specific information and adapt the diagram to illustrate your study design (e.g., changing method of assignment to study group, adding study arms, visits, etc.). The time point(s) indicated in the schematic should correspond to the time point(s) in ***Section 1.3, Schedule of Activities****, e.g., Visit 1, Day 0; Visit 2, Day 30 ± 7; etc.*

Process diagram

Week-1 Screening

- Total n=120
- Obtain informed consent
- Screen potential participants by inclusion and exclusion criteria
- Obtain history, document

Day 0 Operation

- Intervention Group (n=120)

Day 1 Follow-up assessments of study endpoints and safety

- Phy examinations;Vital signs; Blood routine test;Serum chemistry; drainage quality and quantity; drainaige amylase; drainage bacteria culture

Day 3 Follow-up assessments of study endpoints and safety

- Phy examinations;Vital signs; Blood routine test;Serum chemistry; drainage quality and quantity; drainaige amylase; drainage bacteria culture

Day 7 Follow-up assessments of study endpoints and safety

- Phy examinations;Vital signs; Blood routine test;Serum chemistry; drainage quality and quantity; drainaige amylase; drainage bacteria culture

Day 90 End of Study Assessments

- Phy examinations;Vital signs; Blood routine test;Serum chemistry;the situation of drainage and wound

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -7 to -1	Operation Visit 1, Day 0	Visit 2 Day 1	Visit 3 Day3	Visit 4 Day 7	Final Visit 5 Day 90 +/-3 day
Informed consent	X					
Demographics	X					
Medical history	X					
Physical exam (including height and weight)	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Performance status	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
serum chemistry [a]	X	X	X	X	X	X
Pregnancy test [b]	X					
Trial intervention		X				
Intraoperative outcomes [c]		X				
drainage quality			X	X	X	X
drainage quantity			X	X	X	X
drainaige amylase			X	X	X	
drainage bacteria culture			X	X	X	
Adverse event review and evaluation		X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X

a:Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium.
b:Urine pregnancy test (women of childbearing potential).
c: pancreaticojejunostomy time; operative course, final pathology, gland texture, pancreatic duct diameter, size of the stent, length of pancreatic juice in the stent tube, width of the pancreatic stump and diameter of the jejunum

2 INTRODUCTION

2.1 STUDY RATIONALE

Pancreaticoduodenectomy (PD) is one of the most complicated surgical procedure and one of the standard treatments for benign and malignant disease of pancreatic head and periampullary region. The key point of PD is still the enteric reconstruction of pancreatic stump. We established a new digestive reconstruction technique named shark mouth modified pancreaticojejunostomy, which had theoretical advantages including easier performed; lower tension and less complication. So we conduct this trial to evaluate this procedure.

2.2 BACKGROUND

Pancreaticoduodenectomy (PD) is one of the most complicated surgical procedure and one of the standard treatments for benign and malignant disease of pancreatic head and periampullary region. Improvements in surgical techniques and the perioperative management of patients undergoing PD have reduced the surgical mortality rates to less than 3% in high-volume medical centers. However, the incidence of postoperative complication remains high, which ranges from 30% to 50% and the pancreatic fistula rate ranges from 5% to 40%.

Since the ISGPF classification was declared in 2005, it has been widely accepted. The rate of clinically relevant postoperative pancreatic fistula (CR-POPF) continued to persist at approximately 15%.The CR-POPF is one of the most important life-threatening complications that could lead to intra-abdominal abscess, hemorrhage, and sepsis. The exocrine output from the pancreatic remnant was now widely implicated as the initial cause of fistula. The underlying process is the continuous leakage of caustic proteases and lipolytic enzymes, with significant local consequences (abscess, pancreatic fistula, acute pancreatitis, pseudoaneurysm) and systemic sequelae (sepsis, shock, pulmonary insufficiency). So the clinically significant pancreatic fistula symptoms were caused by enzyme leakage and inflammation including bacterial and non- bacterial inflammation. The enzyme may be the initial promoting factor but the inflammation facilitated by enzyme was another important factor in the development of pancreatic fistula. The higher body weight, undilated main pancreatic duct and soft gland were widely accepted as the risk factors of CR-POPF and all these patient factor couldn't be changed by the surgeons. So the feasible and easy way to decrease the CR-POPF is to improve the enteric reconstruction technique of pancreatic stump.

There were different techniques of enteric reconstruction, including: invagination pancreaticojejunostomy, binding pancreaticojejunostomy, duct-to-mucosa pancreaticojejunostomy, Roux-en-Y pancreaticojejunostomy, and pancreaticogastrostomy and each technique had its advantages and disadvantages. Several anastomotic surgical techniques have been developed to reduce the incidence of pancreatic fistula in recent decades, including, Peng's binding method, Bulgmart Method. Large prospective studies and meta-analyses show no significant differences in postoperative complications and mortality among these reconstruction methods. Invagination pancreaticojejunostomy and duct-to-mucosa pancreaticojejunostomy are the most popular technique of pancreaticojejunostomy. However invagination pancreaticojejunostomy is difficult to perform in the situation of larger pancreatic remnant and soft gland. Duct-to-mucosa pancreaticojejunostomy is difficult to perform in the situation of thinner pancreatic duct and the uncompleted drainage of the pancreatic remnant is also considered to be the important reason of CR-POPF.

Theoretically, the incision of "Shark Mouth" might facilitate the pancreaticojejunostomy especially for the large pancreatic remnant; the feature of anastomosis might reduce the tension of pancreaticojejunostomy, which is important for the healing of anastomosis and might reduce the risk of POPF in the soft pancreas; the characters of anastomosis permits total drainage of pancreatic remnant, which is crucial in the situation of thinner pancreatic ducts. The purpose of this study is to evaluate the new anastomosis called "Shark Mouth Modified Pancreaticojejunostomy", especially the morbidity of POPF.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The main risks for study patients are the occurrence of postoperative pancreatic fistula and other complications after the performance of the shark mouth modified pancreaticojejunostomy. The rest potential risks are related with the rest clinically established standard surgical procedures.

2.3.2 KNOWN POTENTIAL BENEFITS

The main potential benefit for study patients is reducing the occurrence of postoperative pancreatic fistula as well as other complications after the performance of the shark mouth modified pancreaticojejunostomy. All rest surgical procedures carried out are clinically established standard procedures.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The newly established digestive reconstruction technique named shark mouth modified pancreaticojejunostomy has theoretical advantages including easier performed lower tension and less complication. Thus we performed the current clinical trial to investigate the clinical efficacy of the shark mouth modified pancreaticojejunostomy.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the new procedure shark mouth modified pancreaticojejunostomy (SMMP)	*Postoperative pancreatic fistula (POPF) occurrence rate.*	*Postoperative pancreatic fistula (POPF) is one of the most frequent and ominous complications after PD, which is somehow related with the anastomosis technique*
Secondary		
To popularize SMMP.	*Anastomosis time* *Morbidities besides the POPF*	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Postoperative hospital stay	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a prospective observational study evaluating the clinical efficacy of shark mouth modified pancreaticojejunostomy. The study will enroll a total of 120 participants who need to undergo the pancreaticoduodenectomy and will last for 2 years. The patients will underwent the shark mouth modified pancreaticojejunostomy procedure and be followed up. The primary endpoint of the study is the incidence of postoperative pancreatic fistula. The secondary endpoint is the postoperative hospital stay, morbidity, and the anastomosis time of the pancreaticojejunostomy procedure.

4.2 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit at 3 months after the operation.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients who meet the following criteria will be included in the study:

1.Patients diagnosed with pancreatic cancer or other diseases which need pancreaticoduodenectomy

2.Operation-tolerated

3.Informed consent

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. History of abdominal operation

2. Pancreaticoduodenectomy is given up during operation

3. Patients require to exit from the study anytime

4. Pregnancy

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Posters will be displayed in the outpatient and inpatient departments of Peking University Third Hospital in order to enroll the potential participants. The brief introduction of the clinical trial and the contact information will be printed on the posters.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The SMMP will be performed according to the standard procedure. The remnant of jejunum is closed by continuous suture. The transverse incision is made on the posterior wall of the jejunum (5 centimeters distal to remnant), which starts at 0.2 centimeter to the mesenteric border and should never exceed the anti-mesenteric border . In case of large pancreas remnant, a longitudinal jejunum incision will be done at anterior part of anastomosis.The posterior part of anastomosis is two layers of intermittent suture, including seromuscular suture layer and full thickness suture layer. The anterior part of anastomosis is a single layer full thickness suture. At last, the seromuscular layer of the proximal jejunum is sutured with the anterior pancreatic capsule to cover the anterior part of anastomosis.

6.2 STUDY INTERVENTION COMPLIANCE

The compliance will be assessed by the records of the follow up information.

6.3 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are

concomitant prescription medications, over-the-counter medications and supplements. The use of somatostatin, somatostatin analogs, antibiotics and acid inhibitors should be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from SMMP does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).The data to be collected at the time of study intervention discontinuation .

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients can withdraw from the trial at their own request or at the request of their legal representative at any time. Patients may be removed if, in the investigator's opinion, continuation of the trail could be detrimental to the patient's well-being or if a PD is not performed due to technical unresectability, metastatic disease, or other reasons. Every withdrawal will be recorded in the clinical report forms (CRFs) and in the patient's medical case records. All examinations scheduled for the final trial day will be performed on all patients and documented. All data will be analyzed according to the intention-to-treat (ITT) principle.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits on 3 weeks and 3 weeks after the operation is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:
•The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
•Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
•Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

All outcome variables will be evaluated according to internationally accepted standards and scoring systems if available, i.e. the consensus definitions for pancreatic fistula of the International Study Group of Pancreatic Surgery (ISGPS).

The efficacy of the shark mouth modified pancreaticojejunostomy will be comprehensively assessed by the symptoms (e.g. febrile, abdominal pain, exsufflation), signs (e.g. tenderness, rebound tenderness, increased amount of drainage fluids), laboratory examinations of the blood (e.g. amylase), drainage fluids (e.g. amylase), and imaging examinations (e.g., abdominal CT scanning).

8.2 SAFETY AND OTHER ASSESSMENTS

The safety of the shark mouth modified pancreaticojejunostomy will be comprehensively assessed by the following：

- the vital signs (e.g. temperature, heart rate, respiratory rate and blood pressure),
- laboratory examinations of the blood (e.g. blood routine test, liver function).

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the shark mouth modified pancreaticojejunostomy, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

•**Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
•**Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
•**Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

•**Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
•**Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The study monitor from the Ethics Committee of Peking University Third Hospital will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs

occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study monitor from the Ethics Committee of Peking University Third Hospital will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

In case of AEs, the AEs should be reported in 24 hours to the study main sponsors and ethics committee by telephone or fax. And the AEs records should be submitted in 24 hours.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the local medical administration ministry and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as the local medical administration ministry requests.

8.3.7 REPORTING OF PREGNANCY

Pregnant patients will be excluded from the current trial.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

•Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
•Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
•Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the Ethics Committee of Peking University Third Hospital. The UP report will include the following information:

•Protocol identifying information: Protocol title and number, PI's name, and the IRB project number;
•A detailed description of the event, incident, experience, or outcome;
•An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
•A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

•UPs that are serious adverse events (SAEs) will be reported to Ethics Committee of Peking University Third Hospital within 3 days of the investigator becoming aware of the event.
•Any other UP will be reported to the IRB and to Ethics Committee of Peking University Third Hospital within 10 of the investigator becoming aware of the problem.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  The occurrence of POPF.

- Secondary Efficacy Endpoint(s):

  Anastomosis time
  Morbidities besides the POPF
  Postoperative hospital stay

9.2 SAMPLE SIZE DETERMINATION

Sample size calculation is based on the primary endpoint: POPF rate. An assumed absolute risk of 10% difference in POPF occurrence is the appropriate basis for the calculation assuming 10% POPF in the SMMP technique group and 20% in the previous published data (Harnoss JC, Ulrich AB, Harnoss JM et al (2014) Use and results of consensus definitions in pancreatic surgery: a systematic review. Surgery 155:47–57). This calculation yields a total of 108 patients in the SMMP technique group, which assures a power of 80 % at a two-sided level of significance of 5 % (NCSS and PASS 11 (NCSS Statistical Software, Kaysville, UT, USA)). Assuming an expected withdrawal rate of 10 % during the trial, 12 additional patients will be included; therefore, the total sample size required is n = 120 patients.

9.3 POPULATIONS FOR ANALYSES

•Modified Intention-to-Treat Analysis Dataset (e.g., participants who underwent the shark mouth modified pancreaticojejunostomy and have some particular amount of follow-up outcome data)
•Per-Protocol Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period)
•Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

•For descriptive statistics. Categorical data will be presented in numbers with percentages. Continuous data will be presented in means with standard deviations or medians with ranges.
•A two-tailed $P<0.05$ was considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

POPF was defined and graded according to criteria proposed by the International Study Group on Pancreatic Fistula (ISGPF) as amylase-rich fluid (more than threefold greater than the upper limit of serum amylase level) of any measurable volume on or after postoperative day 3. POPF was subclassified into grade A (abnormal laboratory parameters without change in clinical management), grade B (abnormal laboratory parameters with non-invasive change in clinical management) and grade C (abnormal laboratory parameters requiring invasive treatment). In the present clinical trial, we will only calculate the incidence of POPF of the study participants.

Participants who underwent the shark mouth modified pancreaticojejunostomy and have some particular amount of follow-up outcome data (Modified Intention-to-Treat Analysis Dataset) will be analyzed.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Anastomosis time is defined as time from beginning to end of shark mouth modified pancreaticojejunostomy, which is measured by the timer. Morbidities besides the POPF is classified according to the Clavien-Dindo definition as grade I to grade V. Postoperative hospital stay is defined as the length of hospital stay after the operation. As an observational study, no inferial analysis will be performed.

Participants who underwent the shark mouth modified pancreaticojejunostomy and have some particular amount of follow-up outcome data (Modified Intention-to-Treat Analysis Dataset) will be analyzed.

9.4.4 SAFETY ANALYSES

The present study is evaluating the safety endpoint, all of the factors are included in Section 9.4.2-Section 9.4.3. Each AE will be counted once only for a given participant. Severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC). Start date, stop date, severity, relationship, expectedness, outcome, and duration about each AE will be reported. Serious treatment-emergent AEs should be presented either in a table or a listing.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The baseline demographics information includes age, gender, and race. The baseline laboratory measurements include the blood routine test, serum liver function, serum renal function, serum amylase, serum tumor marker and coagulation function test.

9.4.6 SUB-GROUP ANALYSES

The subgroup analyses will be analyzed based on age, sex, the texture of the pancreas, diameter of the main pancreatic duct and the primary diseases.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to administering study intervention. The following consent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be - Ethics Committee of Peking University Third Hospital approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Ethics Committee of Peking University Third Hospital, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or the local medical administration ministry.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Ethics Committee of Peking University Third Hospital. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Ethics Committee of Peking University Third Hospital research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Ethics Committee of Peking University Third Hospital.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Ethics Committee of Peking University Third Hospital. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Ethics Committee of Peking University Third Hospital, for use by other researchers including those outside of the study. Permission to transmit data to the Ethics Committee of Peking University Third Hospital will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Ethics Committee of Peking University Third Hospital with the same goal as the sharing of data with the Ethics Committee of Peking University Third Hospital. These samples could be used to research the causes of <specify condition(s)>, its complications and

other conditions for which individuals with < specify condition(s)> are at increased risk, and to improve treatment. The Ethics Committee of Peking University Third Hospital will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Ethics Committee of Peking University Third Hospital.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Dianrong Xiu , Dr. The director of the Department of General Surgery	*Xue Hong, Dr.*
Department of General Surgery, Peking University Third Hospital	*Peking University Third Hospital Medical Science Research Ethics Committee*
49 North Garden Rd., Haidian District Beijing 100191,P.R.China	*49 North Garden Rd., Haidian District Beijing 100191,P.R.China*
+8615611908135	*+86-010-82265883*
Email: xiudianrong7320@163.com	*Email: bysyec@163.com*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor/National Institutes of Health staff.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

•The monitor from the Ethics Committee of Peking University Third Hospital will conduct the monitoring every 2 weeks throughout the study. Random review of the study data will be performed.
•Independent audits will be conducted by the Ethics Committee of Peking University Third Hospital to ensure monitoring practices are performed consistently across all participating sites.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Our institution will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the record system provided by the Ethics Committee of Peking University Third Hospital. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the completion of the primary endpoint. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is

the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Ethics Committee of Peking University Third Hospital and sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Ethics Committee of Peking University Third Hospital.

10.1.12 CONFLICT OF INTEREST POLICY

This is a clinical research sponsored by the primary investigator, and there was no conflicts to disclose.

10.2 ABBREVIATIONS

The list below includes abbreviations utilized in this template.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CR-POPF	clinically relevant postoperative pancreatic fistula
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PD	Pancreaticoduodenectomy
PI	Principal Investigator
POPF	postoperative pancreatic fistula
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SMMP	Shark Mouth Modified Pancreaticojejunostomy
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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