

# Clinical Study Protocol

**Project Title:** Effect of Negative-Pressure Drainage versus Pancreatic Duct Stenting for Preventing Pancreatitis after Endoscopic Papillectomy for Duodenal Papillary Tumors: A Prospective, Multicenter, Randomized Controlled Trial

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## Protocol Synopsis

<b>Protocol Title</b>	Effect of Negative-Pressure Drainage versus Pancreatic Duct Stenting for Preventing Pancreatitis after Endoscopic Papillectomy for Duodenal Papillary Tumors: A Prospective, Multicenter, Randomized Controlled Trial
<b>Sponsor</b>	Shenzhen Hospital of Southern Medical University
<b>Principal Investigator</b>	Wei Gong
<b>Study Site(s) and Investigator(s)</b>	Department of Gastroenterology, Shenzhen Hospital of Southern Medical University — Wei Gong
<b>Study Population</b>	Patients aged 18–75 years scheduled to undergo endoscopic papillectomy of the major duodenal papilla.
<b>Study Objectives</b>	<p>Primary objective</p> <p>To compare the effectiveness of negative-pressure drainage (experimental group) versus pancreatic duct stenting (control group) in preventing pancreatitis after endoscopic papillectomy (EP).</p> <p>Secondary objectives</p> <p>(1) To compare the incidence of post-EP complications between the two groups;</p> <p>(2) To compare procedure duration and technical success rate between the two groups;</p> <p>(3) To compare length of hospital stay and total hospitalization costs between the two groups;</p> <p>(4) To compare complete (R0) resection rate and en bloc resection rate of EP between the two groups;</p> <p>(5) To compare the incidence of post-EP hyperamylasemia between the two groups.</p>
<b>Study Groups</b>	<p>Experimental group: Negative-pressure drainage group—after EP, endoscopic placement of a negative-pressure drainage tube in the descending duodenum.</p> <p>Control group: Pancreatic duct stent group—after EP, ERCP-guided placement of a pancreatic duct stent.</p>
<b>Study Design</b>	Prospective, multicenter, open-label, randomized controlled trial.
<b>Study Duration</b>	4 years
<b>Sample Size</b>	132 participants
<b>Inclusion Criteria</b>	<p>(1) Age 18–75 years</p> <p>(2) Preoperative diagnosis of duodenal papillary adenoma or early adenocarcinoma (<math>\leq</math>T1a)</p>

	(3) Planned endoscopic papillectomy
<b>Exclusion Criteria</b>	<p>(1) Preoperative diagnosis suggestive of adenocarcinoma <math>\geq</math>T1b;</p> <p>(2) Preoperative imaging suggesting intraductal extension into the pancreatic duct or bile duct <math>\geq</math>20 mm;</p> <p>(3) Lesion diameter &gt;40 mm, adjacent to a diverticulum, or other conditions unsuitable for endoscopic therapy;</p> <p>(4) Familial adenomatous polyposis (FAP);</p> <p>(5) Severe cardiopulmonary disease unable to tolerate anesthesia and endoscopic examination/treatment;</p> <p>(6) Coagulation dysfunction;</p> <p>(7) Pregnancy or lactation.</p>
<b>Efficacy Analysis</b>	<p>Primary outcome: Incidence of pancreatitis after EP.</p> <p>Secondary outcomes: Incidence of other post-EP complications; length of hospital stay and total hospitalization costs; procedure duration and technical success rate; complete (R0) resection rate and en bloc resection rate; incidence of hyperamylasemia after EP.</p>
<b>Safety Analysis</b>	Any adverse medical events occurring after the participant receives treatment that are not included in the efficacy analyses.
<b>Statistical Analysis</b>	<p>Analysis sets</p> <p>The Full Analysis Set (FAS), Per-Protocol Set (PPS), and Safety Set (SS) will be used for statistical analyses.</p> <p>FAS: All randomized participants, regardless of whether pancreatic duct stenting or negative-pressure drainage tube placement is ultimately completed or follow-up is completed.</p> <p>PPS: A subset of the FAS who successfully receive negative-pressure drainage tube placement or pancreatic duct stenting, complete scheduled follow-up, have good compliance, and have no major protocol violations or deviations.</p> <p>SS: Participants who receive at least one study intervention (negative-pressure drainage tube or pancreatic duct stent) and subsequently undergo safety assessment.</p> <p>Statistical analysis will be performed using SPSS version 27.</p>
<b>Follow-up</b>	Participants with successful placement of a pancreatic duct stent or a negative-pressure drainage tube after EP will be followed during hospitalization and at 1 month post-procedure. During follow-up, any participants with symptoms such as abdominal pain, bleeding, or fever will return to the hospital within 24 hours for blood tests and endoscopic evaluation to determine the cause of complications,

	which will be recorded in the CRF.
<b>Statistical Methods</b>	Continuous data will be presented as mean $\pm$ standard deviation ( $\bar{x} \pm s$ ). Between-group comparisons of continuous variables will use the t test. Categorical variables will be compared using the chi-square test and presented as percentages. $P < 0.05$ will be considered statistically significant.
<b>Expected Timeline</b>	4 years

## List of Abbreviations and Definitions

### Abbreviation Definition

<u>FAS</u>	<u>Full Analysis Set</u>
<u>PPS</u>	<u>Per-Protocol Set</u>
<u>SS</u>	<u>Safety Set</u>
<u>EP</u>	<u>Endoscopic Papillectomy</u>
<u>FAP</u>	<u>Familial Adenomatous Polyposis</u>
<u>PD</u>	<u>Pancreaticoduodenectomy</u>
<u>AP</u>	<u>Acute Pancreatitis</u>
<u>ESGE</u>	<u>European Society of Gastrointestinal Endoscopy</u>
<u>ERCP</u>	<u>Endoscopic Retrograde Cholangiopancreatography</u>
<u>AE</u>	<u>Adverse Event</u>
<u>SAE</u>	<u>Serious Adverse Event</u>

## Schedule of Study Procedures

Item	Screening Day –3 to Day 0	Procedure Day Intraoperative	During hospitalization	Follow- up 1 month post-procedure
Informed consent	X			
Demographics	X			
Eligibility criteria	X			
Laboratory tests	X		X	X
Electrocardiogram	X			
Endoscopic examination	X			
Blood pressure and heart rate	X	X	X	X
Case report form (CRF)		X	X	X
Adverse events		X	X	X

### 1. Background

Duodenal papillary tumors account for a relatively small proportion of all gastrointestinal tumors, approximately 5%. However, with the widespread use of upper gastrointestinal endoscopy and endoscopic retrograde cholangiopancreatography (ERCP), the detection rate has been increasing [1,2]. Papillary adenomas may occur sporadically or in patients with familial adenomatous polyposis (FAP), the latter being associated with mutations in the adenomatous polyposis coli (APC) gene [3]. Adenoma is the most common benign papillary tumor;

however, because it follows the adenoma-to-carcinoma sequence [4], the risk of malignant transformation is as high as 25–85%. Therefore, it is regarded as a premalignant lesion [3] that requires close surveillance and early resection to reduce the risk of carcinogenesis.

Endoscopic papillectomy (EP) was first reported in Japan in 1983. In 1993, Binmoeller et al. reported the first large cohort study [5], and EP has gradually become an effective treatment for benign ampullary tumors. EP avoids the surgical risks and postoperative complications associated with pancreaticoduodenectomy (PD), and thus has been increasingly adopted in clinical practice. Nevertheless, postoperative complications may still occur after EP, including pancreatitis, post-procedural bleeding, perforation, and cholangitis, among which acute pancreatitis (AP) is one of the most important risks [6]. To reduce the risk of pancreatitis after EP, the European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends routine prophylactic pancreatic duct stenting after EP [7]. The rationale is to prevent transient obstruction of the pancreatic orifice due to postoperative edema and cautery effect, maintain normal pancreatic juice drainage, and reduce pancreatic duct pressure load, thereby lowering the risk of pancreatitis. However, a meta-analysis by Chandan et al. (2024) including 1,858 patients showed similar overall incidences of AP between routine pancreatic duct stenting and no stenting (11.9% vs 16.6%, respectively), without a statistically significant advantage ( $p = 0.4$ ) [8]. A systematic review and meta-analysis by Wang et al. (2019) also suggested that pancreatic duct stenting may reduce the incidence of AP, but the difference did not reach statistical significance (OR = 0.71; 95% CI: 0.36–1.40;  $p = 0.325$ ) [9].

Furthermore, due to local tissue edema, clot obstruction, and bleeding after EP, ERCP-guided pancreatic duct cannulation can be difficult even for experienced endoscopists, leading to failure of pancreatic duct stent placement [10–13]. The reported failure rate of pancreatic duct stent placement can be as high as 30% [14].

When stent placement fails because of difficult cannulation after EP, the incidence of pancreatitis may further increase. In addition, repeated cannulation attempts may exacerbate mechanical irritation and inflammatory response of the pancreatic duct, thereby increasing the risk of AP [15]. To address various difficulties in pancreatic duct stent placement after EP, Desilets and colleagues proposed preoperative pancreatic duct stenting strategies, such as preoperative dual sphincterotomy with pancreatic duct stent placement [11], preoperative placement of an insulated plastic pancreatic duct stent [16], and deep preoperative placement of a pancreatic duct stent with postoperative suture adjustment of stent position [17]. These techniques have, to some extent, improved post-procedural stent placement success and reduced pancreatitis. However, they remain complicated and may be associated with stent migration and post-procedural bleeding. Further optimization of postoperative pancreatic juice drainage remains a key research focus.

To address this clinical problem, the present study innovatively proposes a strategy of negative-pressure drainage in the descending duodenum as an alternative to conventional pancreatic duct stenting, aiming to reduce the incidence of pancreatitis and other complications after EP. In this approach, a negative-pressure drainage tube is inserted through the nasal cavity and positioned on the anal side of the papilla in the descending duodenum, with the distal end connected to a manually compressed drainage bottle to maintain continuous negative-pressure suction and promote effective drainage of pancreatic juice. This strategy not only avoids potential mechanical injury caused by pancreatic duct cannulation but also simplifies postoperative management. Theoretically, it may reduce the incidence of post-EP pancreatitis, decrease procedural difficulty, and reduce related complications.

Recently, our center has applied negative-pressure suction in postoperative management after EP in multiple cases. Preliminary clinical observations have shown good recovery and no significant complications, supporting the feasibility of this strategy and providing a practical foundation for subsequent systematic efficacy

evaluation. However, to date, no systematic studies have been reported domestically or internationally, and the clinical safety and effectiveness of this approach require further validation. Therefore, we plan to conduct a multicenter randomized controlled trial to evaluate the role of negative-pressure drainage versus pancreatic duct stenting in reducing the risk of post-EP pancreatitis, optimizing perioperative management, and reducing postoperative complications, thereby providing new evidence for postoperative management after EP.

## **2. Study Objectives**

### **2.1 Primary Objective**

To compare the effectiveness of negative-pressure drainage (experimental group) versus pancreatic duct stenting (control group) in preventing pancreatitis after endoscopic papillectomy.

### **2.2 Secondary Objectives**

- (1) (1) To compare the incidence of post-EP complications between the two groups;
- (2) (2) To compare procedure duration and technical success rate between the two groups;
- (3) (3) To compare length of hospital stay and total hospitalization costs between the two groups;
- (4) (4) To compare complete (R0) resection rate and en bloc resection rate of EP between the two groups;
- (5) (5) To compare the incidence of post-EP hyperamylasemia between the two groups.

## **3. Study Endpoints**

### **3.1 Primary Endpoint**

Incidence of pancreatitis after EP.

### **3.2 Secondary Endpoints**

- (1)(1) Incidence of other post-EP complications;
- (2)(2) Procedure duration and technical success rate;

- (3)(3) Length of hospital stay and total hospitalization costs;
- (4)(4) Complete (R0) resection rate and en bloc resection rate of EP;
- (5)(5) Incidence of post-EP hyperamylasemia.

## **4. Study Design**

This is a prospective, multicenter, open-label randomized controlled trial. The study will be conducted in accordance with the CONSORT-AI guideline and the Declaration of Helsinki. After written informed consent is obtained, patients meeting the inclusion/exclusion criteria will be screened. Eligible participants will then be randomized in a 1:1 ratio to the experimental group (negative-pressure drainage after EP) or the control group (pancreatic duct stenting after EP). Participants will be treated according to the assigned treatment regimen.

### **4.1 Randomization and Blinding**

#### **4.1.1 Randomization**

In this study, patients meeting the inclusion/exclusion criteria will be assigned in a 1:1 ratio to the experimental group (negative-pressure drainage group) and the control group (pancreatic duct stent group). The random sequence will be generated by concealed allocation at each participating center in blocks of 10 participants. Randomization will be performed after the patient signs the informed consent form.

#### **4.1.2 Blinding/Unblinding**

Because the two interventions (placement of a negative-pressure drainage tube versus placement of a pancreatic duct stent) differ inherently in their procedures (e.g., device configuration and visibility of an external drainage tube), blinding of the operating endoscopist and participants is not feasible; therefore, the trial will be conducted in an open-label manner. Imaging assessments and data analyses will be performed by other medical professionals independent of the study.

## **5. Study Population**

The study population consists of patients scheduled to undergo endoscopic papillectomy of the duodenal papilla.

**Patients eligible for endoscopic resection of duodenal papillary tumors**

**according to the 2021 ESGE guideline, the 2015 ASGE guideline, etc.**

## **5.2 Inclusion Criteria**

- (1) Age 18–75 years
- (2) Preoperative diagnosis of duodenal papillary adenoma or early adenocarcinoma ( $\leq T1a$ )
- (3) Planned endoscopic papillectomy

## **5.3 Exclusion Criteria**

- (1) Preoperative diagnosis suggestive of adenocarcinoma  $\geq T1b$ ;
- (2) Preoperative imaging suggesting intraductal extension into the pancreatic duct or bile duct  $\geq 20$  mm;
- (3) Lesion diameter  $> 40$  mm, adjacent to a diverticulum, or other conditions unsuitable for endoscopic therapy;
- (4) Familial adenomatous polyposis (FAP);
- (5) Severe cardiopulmonary disease unable to tolerate anesthesia and endoscopic examination/treatment;
- (6) Coagulation dysfunction;
- (7) Pregnancy or lactation.

## **5.4 Withdrawal Criteria**

If a participant withdraws from the study for any reason, the reason must be recorded, including but not limited to:

- 1) Withdrawal of informed consent;
- 2) Study termination by the sponsor;
- 3) Serious adverse events affecting the participant's ability to continue participation;
- 4) Serious protocol violations/deviations;
- 5) Pregnancy;
- 6) Poor compliance;
- 7) Loss to follow-up;
- 8) The investigator and/or sponsor considers that the participant's medical

condition may jeopardize participant safety or that continued participation may be detrimental to the participant's health;

9) Death;

10) Other reasons.

## **5.5 Termination Criteria**

If any of the following occurs, the principal investigator shall submit a termination application to the ethics committee within 24 hours and terminate the study immediately after approval.

### **(1) Abnormally increased incidence of postoperative complications (terminate if any criterion is met)**

1) Incidence of acute pancreatitis after the procedure in the control group >30%. 2) Incidence of pancreatitis and/or other major complications (bleeding, perforation, cholangitis, etc.) after the procedure in the experimental group is higher than that in the control group. 3) Cumulative incidence of complications in the experimental group exceeds the empirical threshold of 50%.

### **(2) Early termination based on interim analysis**

After key follow-up has been completed for 66 participants, an independent statistician will compare the incidence of pancreatitis after the procedure between the two groups; if two-sided  $p < 0.05$ , an application for early termination may be proposed.

### **(3) Major protocol deviations or defects**

Major deviations, design defects, or operational errors that cannot be corrected by revision or training and that seriously affect data integrity or participant safety.

### **(4) Requirements from regulatory or ethics bodies**

Termination or suspension requested by the sponsor, ethics committee, or regulatory authorities based on ethical, safety, or regulatory considerations.

## **6. Treatment Technique or Device**

### **6.1 Study Devices**

The negative-pressure drainage tube is made of flexible polymer material

and is a transparent or semi-transparent white tubular device, with functions including adjustable negative pressure, water/air infusion, and continuous suction. Each product is supplied in sterile packaging, with the product name, model, batch number, and expiration date clearly indicated on the package and label. In clinical practice, similar devices such as a nasogastric tube, jejunal feeding tube, or intestinal obstruction tube may be flexibly selected, without restriction to specific brands or models.

The pancreatic duct stent is a routinely used stent product, mostly made of silicone or medical-grade polymers, in a slender tubular shape, generally blue or green in color. The packaging complies with national standards for medical devices, and the label also indicates detailed product information. The brand, diameter, and length of the pancreatic duct stent are not restricted and will be determined by the operating endoscopist according to the patient's condition.

Supportive or rescue drugs and devices used during the study for prevention, diagnosis, or treatment purposes, or as part of standard therapy for a diagnosed disease, are considered non-investigational products.

After endoscopic papillectomy, participants in both groups will receive different device-based interventions:

Negative-pressure drainage group: After EP, a negative-pressure drainage tube will be inserted through the nasal cavity and positioned on the anal side of the papilla in the descending duodenum. The distal end will be connected to a manually compressed drainage bottle to maintain continuous negative-pressure suction and promote effective drainage of pancreatic juice. Negative pressure parameters will be adjusted according to the clinical condition to achieve timely drainage of pancreatic juice and duodenal contents. If there are no obvious complications after EP, the tube will be removed on postoperative day 3. If signs of complications such as persistent massive bleeding or device-related perforation occur intraoperatively, rescue intervention will be initiated immediately: a pancreatic duct stent will be placed, and a negative-pressure drainage tube will also

be placed to continue drainage. The timing of stent removal will follow the stent removal procedure for the control group.

Pancreatic duct stent group: Conventional ERCP-guided pancreatic duct stent placement will be performed. The pancreatic duct stent will be removed endoscopically within 1 month post-procedure. All procedures will be performed by experienced endoscopists according to standard operating procedures. If the number of stent placement attempts is  $\geq 3$  or cumulative cannulation time exceeds 15 min, placement will be considered a failure and will be immediately converted to placement of a negative-pressure drainage tube; the tube position and removal timing will follow the experimental group protocol.

Whether to place a biliary stent is not restricted in either group and will be decided by the operating endoscopist based on the patient's condition.

**If severe device-related adverse events occur during treatment (e.g., persistent massive bleeding, severe pancreatitis, device-related perforation, or obvious device malfunction), the relevant device should be discontinued immediately, and the participant may be withdrawn from the study as appropriate to ensure safety.**

**Information on all concomitant medications during the study (generic name, indication, dose, and administration time, etc.) must be recorded in detail in the case report form. Use of other investigational drugs from other clinical trials is prohibited during the study.**

**All devices should be kept in intact packaging with clearly legible labels. Devices must be stored in a temperature-controlled, dry environment away from direct sunlight. Packaging integrity and expiration date should be checked before use; devices with abnormalities must not be used and should be reported promptly.**

**Devices will be managed centrally by designated personnel. Prior to dispensing, packaging integrity and expiration date must be checked, and dispensing records must be maintained. All operators must receive dedicated training to ensure device use complies with standard operating procedures.**

**At the end of the study or when safety concerns arise, unused or expired investigational devices must be strictly collected and properly destroyed in accordance with hospital and regulatory requirements. The collection process must record the model, batch number, quantity, and date to ensure all devices are managed in a standardized manner and do not enter the market.**

## **7. Study Methods and Procedures**

All participants must sign the informed consent form before screening; only those who meet the inclusion criteria may enter the study.

Participants will be randomized into two groups: the negative-pressure drainage group (experimental group) and the pancreatic duct stent group (control group).

All participants will undergo endoscopic papillectomy (EP), and during the procedure, a negative-pressure drainage tube or a pancreatic duct stent will be placed according to randomization. All participants will fast for 48 hours after the procedure and receive intravenous fluids and nutritional support, as well as relevant medications for prevention of infection, pancreatitis, and bleeding. After 48 hours, if imaging and clinical indicators are normal, diet will be advanced gradually from clear liquids to a soft diet, and parenteral nutrition will be continued as needed until oral intake is restored.

During treatment, safety and efficacy endpoints will be assessed at predefined time points, including incidence of pancreatitis after the procedure, EP-related complications, length of hospital stay and costs, procedure duration, device technical success rate, complete (R0) resection rate and en bloc resection rate, and incidence of hyperamylasemia after EP.

Follow-up will be performed at 1 month after enrollment, and clinical status and quality-of-life data will be collected. Treatment will continue until the participant enters the follow-up period or meets any withdrawal criterion.

### **7.1 Screening Period**

All participants must complete screening examinations before enrollment and will be screened according to the inclusion/exclusion criteria.

- (1) Sign the informed consent form;
- (2) Record demographic information: date of birth, sex, initials;
- (3) Obtain detailed medical history and perform a physical examination (including vital signs, height, weight, and systemic examination);
- (4) Complete baseline laboratory tests: complete blood count, biochemical tests, coagulation profile, urinalysis, stool routine test (fecal occult blood), etc.;
- (5) As clinically indicated, perform relevant imaging examinations (e.g., abdominal ultrasound or CT) to exclude other indications;
- (6) Eligible participants meeting criteria will enter the randomization stage.

## **7.2 Treatment Period**

Eligible participants will undergo endoscopic papillectomy (EP) on the day of the procedure, performed by senior endoscopists. After completion of EP, participants will be allocated into the following two groups according to 1:1 randomization:

### **7.2.1 Control Group (Pancreatic Duct Stent Group, Figure A)**

- Immediately after EP, a prophylactic plastic pancreatic duct stent will be placed under dual monitoring by endoscopy and fluoroscopy. The model and length will be determined by the endoscopist based on preoperative imaging assessment. Placement of a biliary stent is not restricted.
- If the number of stent placement attempts is  $\geq 3$  or cumulative cannulation time exceeds 15 min, placement will be considered a failure and will be immediately converted to placement of a negative-pressure drainage tube; the tube position will follow the experimental group protocol.
- For participants with successful stent placement, the stent will be removed endoscopically within 30 days after the procedure; for those converted to negative-pressure drainage tube placement, the tube will be removed after assessment at 72 h post-procedure confirming no complications.

### **7.2.2 Experimental Group (Negative-Pressure Drainage Group, Figure B)**

- After EP, a negative-pressure drainage tube will be inserted through the nasal cavity and its tip positioned on the anal side of the papilla in the descending duodenum. The distal end will then be connected to a manually compressed drainage bottle to continuously drain pancreatic juice and duodenal contents.
- If signs of complications such as persistent massive bleeding or device-related

perforation occur intraoperatively, rescue intervention will be initiated immediately: a pancreatic duct stent will be placed, and a negative-pressure drainage tube will also be placed to continue drainage.

- For participants with successful placement of the negative-pressure drainage tube, the tube will be removed after assessment at 72 h post-procedure confirming no significant complications; for those converted to pancreatic duct stent placement, stent removal will follow the control group procedure.

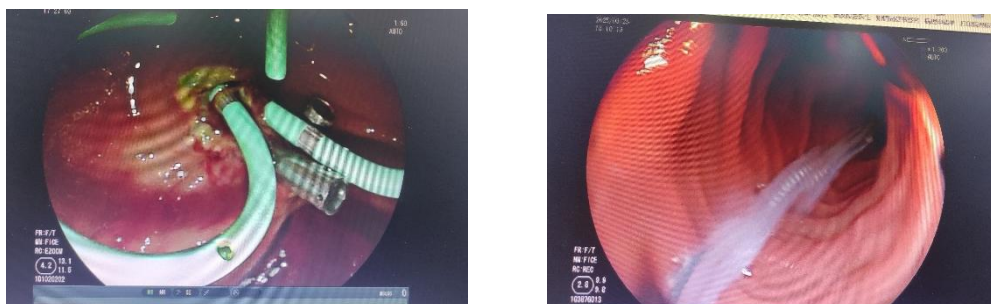


Figure A. Placement of a conventional pancreatic duct stent and biliary stent  
Figure B. Placement of a negative-pressure drainage tube

### 7.3 Follow-up Period

(1) After completion of treatment, all participants will enter the follow-up period, including follow-up during postoperative hospitalization and at 1 month post-procedure.

(2) Record clinical status and complications during hospitalization and within 1 month after the procedure in both groups; collect relevant laboratory tests (e.g., serum amylase, lipase, CRP, liver function, etc.). In the control group (pancreatic duct stent group), the stent will be removed endoscopically within 1 month after the procedure, and the removal process and related complications will be recorded. In the experimental group (negative-pressure drainage group), the drainage tube will be removed on postoperative day 3 if there are no complications, and drainage tube function, displacement, obstruction, etc. will be recorded.

(3) Follow-up data will be used for statistical analyses to compare differences in efficacy and safety endpoints between negative-pressure drainage and pancreatic duct stenting;

(4) Based on follow-up results, investigators will further evaluate the long-term benefits and risks of the two strategies, providing scientific evidence to optimize postoperative management after EP.

## 8. Outcome Measures

### 8.1 Efficacy Assessments

- Incidence of pancreatitis after EP in the negative-pressure drainage group vs the pancreatic duct stent group
  - Incidence of other complications
  - Length of hospital stay and total hospitalization costs
  - Procedure duration and technical success rate
  - Complete (R0) resection rate and en bloc resection rate of EP
  - Incidence of hyperamylasemia after EP
- 1) Acute pancreatitis (AP): defined according to the revised 2012 Atlanta Classification [18], requiring at least 2 of the following 3 criteria: (1) persistent upper abdominal pain; (2) serum amylase or lipase at least three times the upper limit of normal; (3) characteristic findings of AP on computed tomography.
  - 2) Severity of AP: Based on the revised 2012 Atlanta Classification, AP is categorized as mild, moderately severe, or severe according to the presence and duration of organ failure and local or systemic complications.
  - 3) Hyperamylasemia: postoperative serum amylase above the upper limit of normal without clinical symptoms, and imaging excludes acute pancreatitis.
  - 4) Other post-EP complications: includes bleeding, perforation, and cholangitis after EP.
    - a) Post-EP bleeding: hematemesis, melena, or hematochezia after EP, with a decrease in hemoglobin  $\geq 2$  g/dL compared with baseline, or requiring blood transfusion or endoscopic hemostasis.
    - b) Post-EP perforation: a perforation identified during or after EP, or imaging evidence of free air.
    - c) Post-EP cholangitis: postoperative fever with elevated inflammatory markers and imaging evidence of bile duct dilation or infection, requiring antibiotic therapy.
    - d) Incidence of post-EP complications: the proportion of participants who

develop any of the above complications.

- 5) Complete (R0) resection rate: the proportion of participants with histopathologically negative horizontal and vertical margins.
- 6) En bloc resection rate: the proportion of participants whose lesion is removed in a single piece.
- 7) Procedure duration: time from insertion of the endoscope to completion of the procedure.
- 8) Technical success rate: the proportion of participants in whom the assigned intervention (pancreatic duct stent placement or negative-pressure drainage tube placement) is successfully completed.
- 9) Length of hospital stay: the total number of days hospitalized.
- 10) Total hospitalization costs: the total cost incurred during hospitalization.

## **8.2 Safety Assessments**

Safety assessments include relevant parameters, methods and time points of evaluation, and procedures for recording and reporting adverse events (AEs) and concomitant diseases, including reporting procedures as well as follow-up forms and duration after AE occurrence.

## **9. Safety Monitoring, Reporting, and Medical Management**

### **9.1 Definition of Adverse Events (AEs)**

An adverse event (AE) refers to any unfavorable medical occurrence in a patient or participant after receiving a study device, which does not necessarily have a causal relationship with the treatment. Therefore, an AE may be any unfavorable sign (including abnormal laboratory findings), symptom, or disease temporally associated with use of the device, whether or not considered related to the investigational device. AEs include serious adverse events (SAEs) and non-serious adverse events.

### **9.2 Definition of Serious Adverse Events (SAEs)**

A serious adverse event (SAE) is any adverse event that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or causes a

congenital anomaly/birth defect. Additionally, other important medical events that may not result in death or hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed above are also considered SAEs.

#### 9.2.1 Death

Death refers to a participant's death from any cause during the study.

#### 9.2.2 Life-threatening event

A life-threatening event refers to an event in which the participant was at immediate risk of death at the time of the event.

#### 9.2.3 Hospitalization or prolongation of hospitalization

Hospitalization refers to admission to a hospital for treatment or observation, or prolongation of existing hospitalization due to an adverse event.

### **9.3 Recording, Collection, Reporting, and Management of Adverse Events**

#### **9.3.1 Collection, Reporting, and Management of AEs**

From signing informed consent until completion of follow-up (1 month after the procedure), all adverse events occurring in participants must be recorded and evaluated.

All adverse events should be documented in the case report form, including time of occurrence, severity, duration, outcome, and measures taken. The severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Investigators should determine the causal relationship between the AE and the study intervention.

#### **9.3.2 Management and Handling of AEs**

##### 9.3.3 Collection and Reporting of SAEs

**All serious adverse events (SAEs) must be reported to the sponsor and the ethics committee within 24 hours, and relevant information should be recorded in detail.**

SAE reports should include the participant's identification code, a description of the event, time of onset, severity, outcome, treatment measures, and the investigator's

assessment of causality.

#### **9.3.4 Treatment of AEs/SAEs**

Participants experiencing AEs/SAEs should receive appropriate medical treatment according to clinical needs. Study interventions may be discontinued, modified, or additional treatments may be provided as necessary to ensure participant safety.

##### **●9.3.5 Pregnancy**

●If pregnancy occurs during the study, the participant should be withdrawn immediately and the pregnancy should be reported as an SAE within 24 hours. The pregnancy outcome should be followed until completion.

●All clinical laboratory tests will be performed by the clinical laboratory of the participating hospital and will comply with relevant laws and regulations.

##### **●Quality Control and Assurance of Laboratory Testing**

##### **●9.3.6**

#### **9.3.5 Other Responsibilities of the Investigator During Follow-up of Serious Adverse Events**

Based on clinical judgment, the investigator should conduct appropriate evaluations and provide necessary treatment for the SAE, including (but not limited to) clinically indicated laboratory tests and physical examinations. Any results of such evaluations, or any newly available or updated information related to the SAE, must be submitted as follow-up reports; the timelines and procedures for follow-up reporting are the same as those for the initial SAE report.

#### **9.3.6**

### **10. Criteria for Trial Termination/Suspension**

The sponsor has the right to terminate/suspend this trial. Before terminating or suspending a clinical trial, the sponsor shall notify the investigators, the ethics committee, and the medical device clinical trial management department, and state the reasons. After early termination/suspension, restarting the study requires ethics committee approval.

Termination/Suspension as required by the Ethics Committee.

### **11. Criteria for Completion of the Clinical Trial**

The trial will end when all participants meet the following conditions:

- 1) All participants have completed at least 1-month follow-up;
- 2) Or all participants have died, are lost to follow-up, or have withdrawn informed consent.

## **12. Data Management**

### **12.1 Data Management**

- 1) Investigators must ensure that data are truthful, complete, and accurate;
- 2) Any correction to trial records must be made by striking through the original entry, writing the corrected data in the margin, stating the reason, and signed and dated by the investigator; erasing or overwriting the original record is not allowed;
- 3) Laboratory test items must be complete.

### **12.2 Data Recording and Document Retention**

Subject data on the case report form shall be recorded using subject codes; subjects may be identified only by their subject code or initials.

Clinical data will be stored by data management personnel on an encrypted laboratory computer. After data are confirmed to be free of queries, all parties will sign the database lock request form, and the data manager will lock the database. After database lock, the data manager will export the analysis dataset and provide it to the statistician for statistical analysis. Locked data cannot be edited. Any issues identified after database lock, once confirmed, may be corrected within the statistical analysis programs.

## **13. Statistical Analysis**

### **13.1 Sample Size Calculation**

This study is a prospective randomized controlled trial (RCT) designed to evaluate the effectiveness of negative-pressure drainage in preventing pancreatitis after endoscopic papillectomy (EP). According to the study by Jiang et al., the incidence of acute pancreatitis after EP in the pancreatic duct stent group was 31%. Considering that the characteristics of our study population and real-world clinical practice are similar, an event rate of 30% is used as the control-group event rate for sample size estimation. The expected event rate in the experimental group

(negative-pressure drainage group) is 10%. Sample size parameters were set as follows: significance level  $\alpha = 0.05$  (two-sided), power  $1-\beta = 80\%$ , and allocation ratio  $R = 1$  (i.e., 1:1 randomization). Using PASS 15 software, the results indicated that 62 participants per group are required. Considering a 5% dropout rate in practice, the final total sample size is 132 participants, i.e., 66 participants per group.

### 13.2 Statistical Analysis

**The significance level is set at  $\alpha = 0.05$  (two-sided), and all hypothesis tests are two-sided. Continuous data will be described as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). Between-group comparisons of continuous variables will use the t test. Categorical variables will be compared using the chi-square test and described as percentages.  $P < 0.05$  will be considered statistically significant.**

To improve study efficiency and ensure participant safety, one interim analysis is planned. After enrollment of 50% of the sample size (i.e., 33 participants per group, 66 in total), a preliminary evaluation of the primary endpoint event (postoperative pancreatitis) will be performed. The interim analysis will use the O'Brien–Fleming boundary method to control the overall type I error rate ( $\alpha = 0.05$ ), with a stringent significance threshold set for the interim stage ( $p < 0.0054$ ) to ensure reliability of statistical conclusions. If the interim analysis demonstrates a significant difference between groups for the primary endpoint and meets the prespecified statistical boundary, the study team will consider early termination of the trial and submit the interim analysis report and recommendation for termination to the ethics committee.

In addition, considering the clinical context and potential practical advantages of the intervention, secondary endpoints will be evaluated concurrently at the interim analysis, including incidence of hyperamylasemia, cannulation success rate, procedure duration, length of hospital stay, and hospitalization costs. If the experimental group does not show a statistically significant difference in the primary endpoint but demonstrates clear clinical advantages in these secondary endpoints, this may also serve as a basis for early termination. The study team will

comprehensively assess efficacy, safety, procedural feasibility, and patient benefit, and will decide whether to end the trial early after thorough deliberation.

The interim analysis will be performed by an independent statistician, and the analysis process will remain blinded to avoid bias affecting subsequent enrollment and interventions. All interim analysis results and decision recommendations will be submitted to the ethics committee for review. The interim analysis design and any potential early termination are premised on safeguarding participants' rights and interests. All decisions will be made strictly based on statistical results and ethical principles to ensure the scientific rigor and fairness of the study.

### **13.3 Definition and Selection of Analysis Sets**

The Full Analysis Set (FAS) includes all enrolled participants who receive at least one study device and have at least one valid efficacy assessment.

The Safety Set (SS) includes all enrolled participants who receive at least one study device and have at least one safety assessment.

The Per-Protocol Set (PPS) includes all cases in the FAS who complete the protocol-specified treatment without major protocol violations.

### **13.4 Statistical Methods**

Analyses will include participant disposition, demographic characteristics and baseline analyses, feasibility and safety analyses, and efficacy analyses.

### **13.5 Statistical Software and General Requirements**

- All statistical analyses will be performed using SPSS v27 or other statistical software.

- Continuous variables will be described using mean, standard deviation, median, minimum, and maximum.

- Categorical variables will be described using frequencies and percentages.

- For this study, the main endpoints (efficacy, postoperative outcomes, and complication rates) will be analyzed using the chi-square test.

## **14. Trial Management**

### **14.1 Compliance with Good Clinical Practice (GCP)**

Trial management organization and implementation of medical device clinical trial management requirements:

- 1) Both the medical device trial applicant and the investigators shall implement a quality control and quality assurance system for the clinical trial using standard operating procedures (SOPs);
- 2) Source documents must comply with China's GCP requirements;
- 3) Laboratory test results must be accurate and reliable;
- 4) All observations and findings must be verified to ensure data reliability;
- 5) Establish a complete trial organizational structure and clarify responsibilities of personnel at all levels;
- 6) The principal investigator will be responsible for overall quality control and for implementing responsibilities at all levels;
- 7) The principal investigator will be responsible for designing the protocol and the informed consent form and implementing the trial after obtaining the consent of the medical device trial applicant. After the trial is completed, the principal investigator will prepare the final study report;
- 8) Designated investigators will be responsible for developing detailed trial implementation procedures and SOPs for use during the trial;
- 9) Before trial initiation, the study team will organize all participants to study the protocol; all trial personnel must receive GCP training;
- 10) Physicians and nurses participating in the trial must strictly comply with the protocol requirements and procedures and must not modify them without authorization;
- 11) Designated statisticians will be responsible for comprehensive statistical processing of the data.

#### **14.2 Protection of Participant Privacy**

All data collected during the trial will be entered into a computer system for confidential storage and analysis. When necessary, relevant institutions may audit the records to verify the truthfulness, accuracy, and completeness of the data. Trial results

may be published in academic journals; however, participants' names will not be disclosed, and participant privacy will be protected.

Additional preventive measures will be taken to ensure confidentiality of documents and to prevent identification of participants based on genetic data. However, under special circumstances, certain individuals may access a participant's genetic data and personal identification code. For example, in a medical emergency, the sponsor, its representative physicians, or investigators may know the participant identification code and have access to that participant's genetic data. In addition, relevant regulatory authorities may require access to related documents.

### **14.3 Problems Occurring During the Trial and Mitigation Measures**

1) Protocol amendments: After ethics committee approval, if amendments are needed, a 'Protocol Amendment Explanation' must be prepared and signed by the principal investigator. Amendments may be made only after agreement between the investigators and the device registration applicant;

2) After protocol amendment, it must be submitted to and approved by the ethics committee before implementation;

3) No trial personnel may deviate from the protocol. If a deviation occurs, an explanation must be written and the device registration applicant notified, who has the right to decide whether the trial should continue;

4) If a participant has a minor protocol deviation, the research staff should notify the device registration applicant promptly and jointly discuss how to handle the deviation and whether the participant should be withdrawn. Minor deviations that do not affect participant safety or protocol integrity are considered minor protocol deviations;

5) Any adverse event (AE) or serious adverse event (SAE) occurring during the trial will be reported and managed in accordance with this protocol and SOPs.

### **14.4 Quality Control and Quality Assurance**

#### **14.4.1 Quality Assurance**

The sponsor, and any collaborating entities entrusted by the sponsor with all or

part of the responsibilities and tasks related to this study (including CROs, SMOs, statistical units, clinical centers, etc.), shall each establish their own quality assurance systems, fulfill their respective responsibilities, and strictly adhere to the protocol, using appropriate SOPs to ensure implementation of the clinical trial quality control and quality assurance system.

#### **14.4.2 Quality Assurance During the Clinical Trial Process**

Before trial initiation, investigators should receive training on the protocol to ensure that the study staff have a thorough understanding of the protocol and the specific meaning of each endpoint. Quality control personnel should verify the basic conditions for conducting the clinical trial to ensure that the trial conditions meet protocol requirements. During the trial, investigators should perform clinical procedures in accordance with the institution's SOPs and protocol requirements, and record data truthfully, promptly, completely, and in a standardized manner. Quality control personnel will perform quality checks of the trial process and relevant source records. After the trial is completed, the study site will organize the project documents, which will be verified by quality control personnel and then archived for retention. The quality assurance department of the clinical research unit will conduct feasibility audits of the trials conducted. When noncompliance is identified, investigators and the responsible person at the site will be promptly notified to correct it, and the correction will be tracked.

#### **14.5 Expected Timeline and Study Completion Date**

- June 2025 to December 2027: Complete patient recruitment, randomization, treatment, and follow-up.
- January 2028 to July 2028: Data statistical analysis.
- August 2028 to June 2029: Manuscript preparation.

#### **14.6 Sponsor Responsibilities**

The sponsor is responsible for initiating, applying for, and organizing this clinical trial and providing trial funding. In accordance with regulations such as the Chinese regulations on medical device clinical trial management and medical device

registration administration, the sponsor will submit the clinical trial application to the China Food and Drug Administration (CFDA), and may also entrust a contract research organization (CRO) to perform certain work and tasks in the clinical trial.

The sponsor selects the clinical trial institutions and investigators, and confirms their qualifications and conditions to ensure completion of the trial.

The sponsor provides the investigational devices to investigators and shall establish a management system and record-keeping system for investigational devices.

#### **14.6.1 Investigator Responsibilities**

This clinical study will be conducted in accordance with the ethical, moral, and scientific principles set forth in the Declaration of Helsinki and China's GCP, as well as the protocol design and requirements.

Investigators are responsible for making medical decisions related to the clinical trial and ensuring that participants receive timely treatment when AEs occur during the trial. Investigators should be familiar with the procedures and requirements for reporting SAEs and record and report such events as required.

#### **14.6.2 Sponsor's Method for Publication of Study Data**

The sponsor has exclusive rights to the study data. Unless written consent is obtained from the sponsor, no individual publication should be made before completion of the final report of the multicenter study. The sponsor has the final decision on manuscripts and publications.

### **15. Trial-Related Ethics**

#### **15.1 Ethics Committee**

Before trial initiation, investigators must submit the investigator's brochure, protocol, informed consent form, investigational device inspection report (as applicable), and any other information provided to participants to the ethics committee for review and approval. Any amendments to the protocol must also be approved by the ethics committee.

#### **15.2 Informed Consent**

Qualified investigators must explain in detail to each participant, as part of the informed consent process, the nature and purpose of the trial, procedures, expected duration, potential risks and benefits, and any possible discomfort. Each participant must understand that participation is voluntary and that he/she may withdraw from the trial and withdraw informed consent at any time without affecting subsequent treatment or the relationship with the treating physician.

The informed consent form should be written in a standard format and, as far as possible, use non-technical language. Each informed consent form must include all of the above information and a statement of voluntariness. The informed consent form must be submitted to the ethics committee for approval.

After explaining the basic content of the trial and confirming that each prospective participant understands the purpose of the trial, the investigator should ask each prospective participant to sign and date the informed consent form. The participant should read and consider the statement before signing and dating, and should receive a copy of the signed informed consent form for retention. Without obtaining informed consent and a signed informed consent form, the participant cannot be enrolled in the trial.

### **15.3 Other**

When a participant is unable to independently participate in the informed consent process, a reliable impartial witness/legal representative must be present throughout the informed consent process. Selection of the impartial witness/legal representative must not infringe upon the participant's confidentiality rights. After the participant provides oral consent, the impartial witness/legal representative should sign and date the informed consent form to certify that the information is accurate.

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## Participant Signature Page

### Informed Consent Statement:

I have been informed of the purpose, background, procedures, risks, and potential benefits of this study. I have had sufficient time and opportunity to ask questions, and I am satisfied with the answers provided.

I have also been informed whom to contact if I have questions, wish to report difficulties or concerns, have suggestions about the study, want further information, or wish to offer assistance to the study. I understand that I may choose not to participate in this study, or may withdraw from the study at any time during the study without giving any reason. In addition, the investigators have not used deception, inducement, coercion, or other means to force me to agree to participate in the study.

I understand that if my condition worsens, or I experience a serious adverse reaction, or my study physician believes that continuing participation is not in my best interest, he/she may decide to withdraw me from the study. The sponsor or regulatory authorities may also terminate the study during the study period without obtaining my consent. If this occurs, the physician will notify me in a timely manner and the study physician will discuss my other options with me.

I have read this informed consent form and agree to participate in this study. I will receive a copy of this informed consent form bearing the signatures of both myself and the investigator.

Participant signature:

Date:

Contact phone number:

Legal representative signature: Relationship: Date:

Contact phone number:

(Note: If the participant lacks or has limited capacity to act, such as inclusion of vulnerable groups with mental disorders or impaired consciousness, the legal representative must sign in the space below.)

Independent witness signature: Date:

Contact phone number:

(Note: An independent witness signature is required only when the participant may have decision-making capacity but is unable to read the text (e.g., illiterate, visually impaired). When a witness is present, the investigator should, if possible, retain video documentation as evidence of informed consent.)

I have accurately explained this document to the participant, he/she has read this informed consent form accurately, and I confirm that the participant had the opportunity to ask questions and voluntarily agreed.

Investigator signature: Date:

Contact phone number: