A Multicenter Randomized Prospective Study on Establishing an ERAS Program and Optimized Clinical Protocol for Patients Undergoing Minimally Invasive Pancreatoduodenectomy (MIPD)

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Principal Investigator Affiliation:
Department of Surgery, Seoul National University Hostpial
Principal Investigator:
Wooil Kwon

Study Overview

Title	A Multicenter Randomized Prospective Study on Establishing an ERAS Program and Optimized Clinical Protocol for Patients Undergoing Minimally Invasive Pancreatoduodenectomy (MIPD)
Principal Investigator	Wooil Kwon Department of Surgery, Seoul National University Hospital
Funding	Korea Health Industry Development Institute (KHIDI)

Objective	To evaluate the impact of an Enhanced Recovery After Surgery (ERAS) program on postoperative recovery in patients undergoing minimally invasive pancreatoduodenectomy (MIPD)
Study Design	A multicenter prospective open-labeled randomized study
Study Period	IRB approval ~ 2027-12-31
Study Population	Patients aged 19 years or older with pancreatic or periampullary tumors scheduled for standard minimally invasive (robotic or laparoscopic) pancreatoduodenectomy
Sample Size	Total N = 140 (ERAS group: 70; Control group: 70)
Vulnerable Subjects	None
Study Methods	Patients scheduled for standard minimally invasive (robotic or laparoscopic) pancreatoduodenectomy for periampullary lesions will be randomized to either the ERAS protocol (ERAS group) or the conventional perioperative protocol (control group). The primary comparison will be the rate of meeting discharge criteria on the afternoon of postoperative day 5. Secondary comparisons include length of hospital stay and incidence of major complications within 30 days postoperatively. Overall operation-related morbidity (Clavien–Dindo classification), postoperative length of stay, and total medical costs (including inpatient, outpatient, and emergency charges from admission through 30 days post-discharge) will also be analyzed.
Efficacy Evaluation	- Primary efficacy analysis: Rate of meeting discharge criteria by the afternoon of POD 5; overall operation-related morbidity (< 30 days) - Secondary efficacy analysis: Length of hospital stay; incidence of major complications within 30 days; medical costs (KRW)
Safety Assessment	All adverse events occurring during the study will be recorded, including assessment of causality with study procedures. Severity, duration,

	management, and relationship to the interventions will be evaluated.
Expected Outcomes	Development of clinical practice guidelines for perioperative management in minimally invasive pancreatoduodenectomy in Korea, demonstrating the effectiveness of the ERAS protocol and establishing a new standard of care. Compared with the conventional protocol, we anticipate improved short-term clinical outcomes and reduced medical costs.

Protocol

1. **Title**

A Multicenter Randomized Prospective Study on Establishing an ERAS Program and Optimized Clinical Protocol for Patients Undergoing Minimally Invasive Pancreatoduodenectomy (MIPD)

Affiliation

1) Seoul National University Hospital: 101, Daehak-ro, Jongno-gu, Seoul
2) SMG-SNU Boramae Medical Center: 20, Boramae-ro 5-gil, Dongjak-gu, Seoul 07061
3) Korea University Anam Hospital: 73 Goryeodae-ro Seongbuk-gu, Seoul 02841

2. **Names and Titles of the Principal Investigator and Co-Investigators**

1) Principal Investigator

Associate Professor, Wooil Kwon

Department of Surgery, Seoul National University Hospital

2) Co-Investigators

Associate Professor, Ho-Jin Lee

Department of Anesthesiology and Pain Medicine, Seoul National University Hospital

Clinical Assistant Professor, Soo-Hyuk Yoon

Department of Anesthesiology and Pain Medicine, Seoul National University Hospital

Clinical Assistant Professor, Hye-Sol Jung

Department of Surgery, Seoul National University Hospital

Clinical Instructor, Young Jae Cho

Department of Surgery, Seoul National University Hospital

Research Nurse, Youngmin Han

Department of Surgery, Seoul National University Hospital

Research Nurse, Hyo-Jin Lee

Department of Surgery, Seoul National University Hospital

Research Nurse, Seulah Park

Department of Surgery, Seoul National University Hospital

Associate Professor, Chang-Sup Lim

Department of Surgery, Seoul National University Boramae Medical Center

Associate Professor, Jung-Man Lee

Department of Anesthesiology and Pain Medicine, Seoul National University Boramae Medical Center

Associate Professor, Young-Dong Yu

Department of Surgery, Korea University Anam Hospital

Clinical Assistant Professor, Yoo Jin Choi

Department of Surgery, Korea University Anam Hospital

Clinical Assistant Professor, Hyunyoung Seong

Department of Anesthesiology and Pain Medicine, Korea University Anam Hospital

3) Study Coordinator

Clinical Instructor, Young Jae Cho

Department of Surgery, Seoul National University Hospital

4) Pharmacist for Investigational Medicinal Products / Device Manager

Not applicable

3. **Sponsor Institution**

1) Name and Address of Sponsor Institution

Department of Surgery, Seoul National University Hospital

101 Daehak-ro, Jongno-gu, Seoul, Republic of Korea 03080

2) Monitoring Staff Name and Title

Research Nurse Hyo-Jin Lee, Department of Surgical Education, Seoul National University Hospital

4. **Funding Source**

Korea Health Industry Development Institute (KHIDI)

- Grant number has not yet been assigned.

5. **Estimated Study Period**

Date of IRB approval ~ December 13, 2027

6. **Target Disease/Condition**

Disease scheduled for minimally invasive pancreaticoduodenectomy

7. **Background and Objectives**

1) **Background**

Since Codivilla first reported pancreatoduodenectomy in 1898, the procedure has evolved, and mortality has decreased to as low as 2%[1]. However, it remains a complex, high-risk operation with postoperative complication rates approaching 40–60%, which impede recovery and drive up healthcare costs. To reduce complications, improved perioperative care protocols were needed[2]. In recent years, numerous studies have explored ways to minimize surgical stress and enhance patient recovery. These efforts led to the development of the Enhanced Recovery After Surgery (ERAS)

protocol, a multimodal pathway designed to reduce postoperative stress, maintain homeostasis, and expedite recovery[3]. Since its introduction, ERAS has demonstrated favorable outcomes across various major surgeries, and the first ERAS guidelines for pancreatoduodenectomy were published in 2012[4,5].

Several studies of ERAS in pancreaticoduodenectomy have shown reductions in postoperative complications, length of stay, and costs[2,3,5-8]. However, research specifically focused on minimally invasive pancreatoduodenectomy remains limited, and evidence for ERAS efficacy in this setting is lacking[2,9,10]. Moreover, no domestic studies have yet addressed ERAS in minimally invasive pancreatoduodenectomy, underscoring the urgent need for a protocol tailored to the Korean context. Therefore, this study aims to evaluate the impact of an evidence-based ERAS protocol on postoperative recovery in patients undergoing minimally invasive pancreatoduodenectomy.

2) Hypothesis and Objectives

A. Hypothesis: In patients undergoing standard minimally invasive pancreatoduodenectomy, those managed with our ERAS protocol will have a significantly higher rate of meeting discharge criteria on the afternoon of postoperative day 5 compared to those managed with the conventional protocol.

B. Objective: To demonstrate the effectiveness of the new ERAS protocol in minimally invasive pancreatoduodenectomy and establish it as the standard perioperative care guideline.

8. **Investigational Medicinal Product Code Name, Generic Name, Raw Material and Quantity, Formulation**

Not applicable

9. **Selection Criteria, Exclusion Criteria, Target Sample Size and Rationale, and Recruitment Plan**

1) **Inclusion Criteria:** Participants must meet all of the following to be eligible:

A. Age ≥ 19 years, scheduled for standard minimally invasive (robotic or laparoscopic) pancreatoduodenectomy for periampullary tumors

B. ECOG performance status of 0 or 1 at screening
C. Able to provide written informed consent, understand study procedures, and complete patient-reported questionnaires
D. ASA physical status classification I-III

2) **Exclusion Criteria:** Participants meeting any of the following will be excluded:
A. Hypersensitivity to fentanyl or ropivacaine
B. Cognitive impairment preventing independent use of patient-controlled analgesia or completion of questionnaires
C. Major internal medical or psychiatric disorders affecting treatment response
D. Severe hepatic or renal dysfunction
E. Any condition deemed inappropriate for study participation by the investigator

3) **Target Sample Size and Rationale**

Sample size was calculated using the StatTools sample size calculator (Stattools.crab.org). Based on previous literature and our clinical experience, we assumed a 30% rate of meeting discharge criteria on the afternoon of postoperative day 5 in the conventional protocol group and a 60% rate in the ERAS group. Using a two-sided test with 80% power, $\alpha = 0.05$, no continuity correction, and accounting for a 10% dropout rate, we determined that 70 patients per arm (total N = 140) are required[11].

4) **Recruitment Plan**

At Seoul National University Hospital, eligible patients aged ≥ 19 years with pancreatic or periampullary tumors scheduled for standard minimally invasive pancreatoduodenectomy who meet inclusion and do not meet exclusion criteria will be informed about the study. Those who voluntarily consent in writing will be enrolled.

10. **Study Methods**

1) Specific Research Methods

A. Screening (Outpatients): When surgery is scheduled in the outpatient clinic, the study coordinator or co-investigator will explain the attached information sheet and informed consent form to the patient and obtain written consent. During screening, the following assessments and investigations will be performed:

i. Evaluation of inclusion and exclusion criteria

ii. Demographic data (sex, age, height, weight, BMI)

iii. Pancreatic cancer staging

iv. Medical/surgical history and concomitant medications relevant to exclusion criteria

v. Randomization immediately after screening. Patients assigned to the ERAS group will receive education using a pre-prepared ERAS protocol leaflet.

vi. Both groups will complete the following patient-reported outcome questionnaires:

   a. Korean-EORTC QLQ C-3015

   b. Korean version of Hospital Anxiety and Depression Scale Anxiety Subscale

B. Perioperative Protocol Details:

The specific perioperative care protocols for each group are as follows.

C. Perioperative Fasting:

i. ERAS group: Per ESPEN guidelines, patients without signs of aspiration risk may consume clear fluids until 2 hours and solid foods until 6 hours prior to anesthesia induction.

ii. Conventional group: Normal regular diet (NRD) on the evening before surgery, with sips of water (SOW) maintained until midnight; then nothing by mouth (NPO) from midnight.

iii. ERAS group: NRD on the evening before surgery; fasting from solid foods starting at midnight. Water is allowed until 3 hours before surgery, and one carbohydrate drink (CarboEn 50, 300 mL, HK Innoen) is taken 2–4 hours pre-operatively.

iv. ERAS group only: On the day of surgery, when consuming CarboEn, patients also receive preemptive analgesia with acetaminophen 650 mg and zaltoprofen 80 mg. The conventional group does not receive preemptive analgesia.

D. Intraoperative Management:

i. Both groups follow Seoul National University Hospital's standard pancreatoduodenectomy protocol.

ii. ERAS group: 8 mg IV dexamethasone at anesthesia induction; ~1 hour before end

of surgery, IV acetaminophen 1000 mg + ibuprofen 300 mg combination and nefopam 20 mg.

iii. Conventional group: 5 mg IV dexamethasone at induction; IV acetaminophen 1000 mg ~1 hour before end of surgery.

E. Postoperative Nutritional Protocol:

i. The ERAS protocol recommends early oral intake. Colorectal ERAS guides diet from 4 hours post-op without increased complications,[12] and gastrectomy ERAS from POD 1.[13] Based on these and our experience, the conventional group currently follows:

ii. Conventional group: Remove Levin tube in the OR immediately after surgery. Begin SOW on the morning of POD 1. After an upright abdominal radiograph on POD 3 morning, if no abnormalities, start soft fluid diet (SFD) on POD 3 evening. After pancreatobiliary CT on POD 4, if no abnormalities, begin soft bland fluid (SBD) at lunch.

iii. ERAS group: Remove Levin tube in the OR. Begin SOW on POD 1 morning. After upright abdominal radiograph on POD 2 morning, if no abnormalities, start SFD on POD 2 evening. After pancreatobiliary CT on POD 3, if no abnormalities, begin SBD at lunch.

F. Postoperative Perianastomotic Drain Management:

i. Numerous studies have examined perianastomotic drainage.[14-18] ERAS recommends drain removal within 72 hours if POD 1 fluid amylase < 5000 U/L.[4] At our center, considering published data, local CT cost/access, and experience, we maintain the following—adopting an ERAS-based removal protocol for the ERAS group:

ii. Conventional group: Two drains placed at hepaticojejunostomy and pancreaticojejunostomy sites. Measure drain fluid amylase on POD 1, 3, and 5; perform pancreatobiliary CT on POD 4. If no issues, remove drains from POD 5 at the surgeon's discretion (based on findings, drain output, fever, pain, etc.).

iii. ERAS group: Same drain placement. Measure amylase on POD 1 and 3; CT on POD 3. If POD 1 amylase ≤ 5000 U/L, amylase is trending down, and CT is clear, remove drains from POD 4. If amylase > 5000 U/L, remove per surgeon's discretion as in conventional group.

iv. In both groups, remove the urinary catheter on POD 2.

G. Postoperative Pain Management Protocol:

1. Both groups use intravenous patient-controlled analgesia (IV-PCA).
2. PACU: If NRS ≥ 5 without nausea/vomiting, give fentanyl 50 μg IV as rescue. If NRS ≥ 5 with nausea/vomiting, give ketorolac 30 mg IV plus metoclopramide 10 mg IV.
3. Ward:
    1. For NRS ≥ 3, patients in both groups are instructed to use the PCA button.
    2. ERAS group: From surgery day through morning of POD 1, IV acetaminophen 1000 mg + ibuprofen 300 mg every 8 hours; from POD 1 morning onward, oral selective COX-2 inhibitor and acetaminophen every 8 hours.
    3. Conventional group: From POD 3 onward, oral acetaminophen 650 mg q8h.
    4. If NRS ≥ 7 persists and no opioid side effects, IV fentanyl 50 μg as first-line rescue. If side effects occur, IV nefopam 20 mg in 50 mL saline over 30 minutes as second-line rescue (only as needed, not exceeding max dose). Failure to control pain leads to study withdrawal.
    5. If nausea/vomiting occurs within 6 hours of prophylactic ramosetron 0.3 mg IV (Nasea®, Astellas), give metoclopramide 10 mg IV; after 6 hours, give ramosetron 0.3 mg IV.
    6. Prohibited: fentanyl patches and non-rescue opioids (nalbuphine, morphine) until POD 3.
    7. Discontinue IV-PCA at lunch on POD 2 in both groups.

Table 1. Key Differences in Perioperative Management Between Groups

Aspect	Conventional Protocol	ERAS Protocol
Preoperative Fasting	NPO (nothing by mouth) of solids and fluids from midnight the day before surgery.	NPO of solids from midnight the day before surgery; clear fluids allowed until 3 hours pre-op; one

		carbohydrate drink (300 mL) consumed 2–4 hours before surgery.
Preemptive Analgesia	Not applied.	With the pre-op carbohydrate drink, patients take acetaminophen 650 mg and zaltoprofen 80 mg orally 2–4 hours before surgery.
Intraoperative Management	– IV dexamethasone 5 mg at anesthesia induction– IV acetaminophen 1 g ~1 hour before end of surgery	– IV dexamethasone 8 mg at anesthesia induction– IV acetaminophen 1 g + ibuprofen 300 mg + nefopam 20 mg ~1 hour before end of surgery
Postoperative Nutrition	– Remove Levin tube in the OR immediately after surgery– POD 1 morning: begin sips of water (SOW)– POD 3 morning: upright abdominal X-ray; if no abnormalities, start soft fluid diet (SFD) on POD 3 evening– POD 4: pancreatobiliary CT; if no findings, start soft bland diet (SBD) at lunch	– Remove Levin tube in the OR immediately after surgery– POD 1 morning: begin SOW– POD 2 morning: upright abdominal X-ray; if no abnormalities, start SFD on POD 2 evening– POD 3: pancreatobiliary CT; if no findings, start SBD at lunch
Postoperative Drain Management	– Two drains placed at hepaticojejunostomy and pancreaticojejunostomy sites– Measure drain fluid amylase on POD 1, 3, and 5– POD 4: pancreatobiliary CT; if no abnormalities, remove drains from POD 5 per surgeon's discretion (based on drain output, fever, pain, etc.)	– Same drain placement as conventional– Measure amylase on POD 1 and 3– POD 4: pancreatobiliary CT; if no abnormalities **and** POD 1 amylase ≤ 5000 U/L **and** POD 3 amylase trending down, remove drains on POD 4– If amylase > 5000 U/L, remove per surgeon's discretion as in conventional group
Postoperative Pain Control	– IV-PCA until ~POD 3– From POD 3 morning: PO acetaminophen 650 mg q8h	– IV-PCA until ~POD 3– Until POD 1 morning: IV acetaminophen 1 g + ibuprofen 300 mg every 8 hr– From POD 1 morning until POD 5: PO acetaminophen 650 mg + zaltoprofen 80 mg q8h

Abbreviations: NPO = nothing by mouth; POD = postoperative day; SOW = sips of water; SFD = soft fluid diet; SBD = soft bland diet; IV-PCA = intravenous patient-controlled analgesia.

2) Allocation and Randomization

1. Allocation Strategy

Randomization will be performed by an independent researcher not involved in the trial, using R software (version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). For each participating site, a block-randomization list with block size 4—containing two control and two ERAS assignments—will be generated and the blocks will be randomly permuted. At each center, subjects will be allocated to control or ERAS in the order specified by this list. The seed number required to reproduce the random sequence will be recorded and kept confidential.

2. Allocation Concealment

The randomization list will be prepared and maintained by a third party not involved in subject enrollment or assessment, ensuring that investigators cannot foresee assignments. Randomization results will then be communicated to the treating team. This is an open-label (non-blinded) study.

3) Investigational Product Administration

Not applicable

4) Observations, Clinical Assessments, and Measurement Methods

A. Baseline and Demographic Data

- Age, sex, height, weight, BMI
- Smoking status
- ASA physical status
- ECOG performance status
- Comorbidities and concomitant medications
- History of prior surgery
- Preoperative neoadjuvant chemotherapy or radiotherapy
- Presence and type of synchronous malignancy

- Dates of hospital admission and planned surgery

B. Intraoperative Data

- Procedure name and duration
- Vascular resection performed (yes/no)
- Estimated blood loss
- Intraoperative fluids and blood products administered
- Use of continuous vasopressor infusion
- Intraoperative adverse events

C. Postoperative Pain Scores

At 4 PM (± 1 hour) on postoperative days (POD) 1–5, pain at rest and on movement will be assessed using the 11-point Numeric Rating Scale (NRS).

D. Total Narcotic Consumption

Cumulative opioid use (morphine-equivalent dose) recorded through POD 5.

E. Time to First Flatus

Hours elapsing from end of surgery to first passage of gas.

F. Postoperative Nausea and Vomiting

On POD 0–5, nausea graded 0 = none, 1 = mild, 2 = requiring antiemetic; record any vomiting episodes.

G. Quality of Recovery

On POD 1–5 at 4 PM (± 1 hour), patient-reported recovery quality via the Korean EQ-5D-5L instrument.

H. Postoperative Complications

All events within 30 days classified by the revised Clavien–Dindo system

and the Comprehensive Complication Index[19,20]

I. Postoperative Pancreatic Fistula (POPF)

Incidence and grade of POPF according to ISGPS definitions[21]

J. Readmission Within 30 Days

Any unplanned hospital readmission within 30 days of discharge.

K. Mortality Within 30 Days

Any death occurring within 30 days of surgery.

L. Discharge-Criteria Fulfillment

At 4 PM (± 1 hour) on POD 5, the proportion of patients who simultaneously meet all of the following:

- Tolerate a soft blended diet for 24 hours
- Ambulate safely without assistance
- Adequate pain control (NRS ≤ 3) on oral non-opioid analgesics only
- Afebrile (< 37.2 ℃) without major complications
- No clinically concerning laboratory abnormalities (e.g., WBC, CRP)

5) Novelty and Differentiation from Existing Studies

To date, no studies have exclusively evaluated ERAS in minimally invasive pancreatoduodenectomy. This trial will develop and assess an ERAS pathway tailored for the increasing application of minimally invasive PD.

6) Subject Benefits and Risks

• Control Group: Standard care as practiced at Seoul National University Hospital; no additional risk beyond routine treatment.

• ERAS Group: Expected to experience shorter length of stay and fewer complications, as reported in other ERAS studies. Risks associated with the ERAS interventions are minimal.

• Any serious adverse event (SAE) will be managed immediately by the principal investigator and reported to the IRB within 24 hours of occurrence.

7) Discontinuation and Withdrawal Criteria

Subjects may withdraw at any time at their own request. The investigator may also discontinue a subject for safety, protocol compliance, or administrative reasons. Upon withdrawal, no further assessments or data collection will occur, though data collected prior to withdrawal will remain in the study database.

8) Safety Evaluation

A. Overview

All ERAS interventions are guideline-recommended and widely used; complication risk is very low.

B. Serious Adverse Events (SAEs)

Defined as Clavien–Dindo grade ≥ 3. SAEs must be reported to the principal investigator within 24 hours and to the IRB within 48 hours.

C. Adverse Event Monitoring

• Record every AE, assess causality with study procedures, and document severity, duration, management, and outcome.

• Monitor planned assessments and any additional testing prompted by clinical findings.

D. Severity Grading

• Mild: Transient, does not interfere with daily activities

• Moderate: Causes some discomfort or interferes with daily activities

• Severe: Prevents performance of daily activities

E. Causality Assessment

Classified as "Unrelated," "Possibly Related," "Likely Related," "Clearly Related," or "Indeterminate," separately for drugs and procedures, based on investigator judgment.

9) Efficacy Endpoints, Analysis Methods, and Interpretation

A. Efficacy Endpoints

1. Primary Outcome: Proportion of patients meeting all discharge criteria on POD 5 afternoon; comparison by chi-square test.
2. Secondary Outcomes:

1. Pain Scores: NRS at rest and on movement from POD 1 to POD 5, analyzed by linear mixed-effects modeling.
2. Nausea/Vomiting Rate: Incidence from POD 0 to POD 5, compared by chi-square test.
3. Total Opioid Use: Compared by Student's t-test or Mann–Whitney U test, depending on distribution.
4. Comprehensive Complication Index: Compared by t-test or Mann–Whitney U test.
5. Clinically Relevant POPF (Grade B+): Incidence compared by chi-square test.
6. Length of Stay (days): Compared by t-test or Mann–Whitney U test.

B. Analysis Populations

1. All Enrolled (Full Analysis Set): All randomized subjects excluding duplicates and ineligible registrations.
2. Modified Intent-to-Treat (mITT): Subjects who underwent the planned minimally invasive surgery after randomization.
3. Per-Protocol (PP): mITT subjects who fully adhered to their assigned perioperative protocol.

The primary analysis will be performed on the mITT set; sensitivity analyses will use the PP set.

C. Definition of Complications

Complications occurring within 30 days post-operatively. They include complications of the carbohydrate drink (e.g., aspiration pneumonia), analgesic agents (e.g., acetaminophen, ketorolac, nefopam, opioids), and surgical complications. Intraoperative AEs will be graded per CTCAE v4.0; postoperative AEs per Clavien–Dindo classification.

1. Clavien-Dindo Classification of Surgical Outcomes

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

2. Clinically Relevant Postoperative Pancreatic Fistula (CR-POPF; ISGPS Criteria as Grade B or C)

Event	BL (NO POPF)	Grade B POPF*	Grade C POPF*
Increased amylase activity > 3 times upper limit institutional normal serum value	YES	YES	YES
Persisting peripancreatic drainage > 3 weeks	NO	YES	YES
Clinically relevant change in management of POPF#	NO	YES	YES
POPF percutaneous or endoscopic specific interventions for collections	NO	YES	YES
Angiographic procedures for POPF related bleeding	NO	YES	YES
Reoperation for POPF	NO	NO	YES
Signs of infection related to POPF	NO	YES, without organ failure	YES, with organ failure
POPF related organ failure^	NO	NO	YES
POPF related death	NO	NO	YES

3. Delayed Gastric Emptying (DGE; ISGPS consensus guidelines)

4. Post-Pancreatectomy Hemorrhage (PPH; ISGPS consensus guidlines)

10) Post-Trial Patient Care and Treatment Standards

All subjects in both the Conventional and ERAS groups will be closely monitored for adverse events during their hospital stay. If pain control is inadequate, "rescue medications" will be administered in-hospital, and upon discharge patients will continue to receive pain management prescriptions at their scheduled surgical outpatient visits as needed.

11) Study Schedule

	PreOP			IntraOP	PostOP						During Admission	PostOP Outpatients
	Pre-registration	Post-registration	PreOP #1		OP Day	POD #1	POD #2	POD #3	POD #4	POD #5		
Informed Consent Explanation	●											
Eligibility Assessment & Study Registration	●											
Baseline Patient Characteristics	●	●										
EORTC QLQ C-30		●										●
Surgery & Anesthesia Data				●								
Discharge-Criteria Assessment										●		
EQ-5D-5L			●			●	●	●	●	●		
Postoperative Pain (NRS)						●	●	●	●	●		
Postoperative Nausea/Vomiting					●	●	●	●	●	●		
Total Opioid Consumption											●	
Time to First Flatus					●	●	●	●	●	●	●	
Urinary Catheter Removal						●	●					
Oral Diet Initiation								●	●			
Drain Removal									●	●	●	
IV-PCA Removal							●					
CT/MRI	●							●	●			
Follow-up for Postoperative Complication					◄							►

1. Registration must occur within 28 days prior to surgery.
2. The day of surgery is defined as Day 0.

3. IV-PCA is discontinued in both groups on POD 2.

4. Oral soft fluid diet begins on POD 3 evening in the Conventional group and POD 2 evening in the ERAS group, provided no fever, pain, or distension, even if first flatus has not occurred.

5. Soft bland diet begins after CT if no abnormalities—on POD 4 lunch in the Conventional group; POD 3 lunch in the ERAS group.

11. Data and Safety Monitoring Plan

1) Monitoring Leadership

• Monitoring Officer: Associate Professor Wooil Kwon
Department of Surgery, Seoul Natinoal University Hospital

• Monitoring Staff: Research Nurse Hyo-Jin Lee
Department of Surgery, Seoul Natinoal University Hospital

2) Monitored Items

- **Study Accruals**

A. Baseline Data: age, sex, BMI, ECOG status, neoadjuvant therapy, comorbidities, alcohol history, medication history, preoperative biliary drainage

B. Intraoperative Data: operation name, operation time, vascular resection, estimated blood loss, fluid, transfusion, vasopressor use, intraoperative events

C. Postoperative Analgesics: types and doses of medications (e.g., fentanyl, NSAIDs, acetaminophen)

D. POD 1-5 Pain Scores

E. POD 0-5 Nausea/Vomiting

F. 30-Day Complications (including POPF)

G. 30-Day Readmissions & Mortality

- **Safety Signals**: consent process, adverse effects from additional analgesics, aspiration risk from carbohydrate loading
-

3) Monitoring Methods & Frequency

A. Safety monitoring for analgesic-related and aspiration events every six months.

B. Periodic review of case report forms for protocol adherence and safety.

C. Monitoring items include:

i. Study progress
ii. Compliance with inclusion/exclusion criteria
iii. Serious adverse events (SAEs)
iv. Protocol deviations
v. Reasons for treatment discontinuation
vi. Integrity of baseline characteristics
vii. Other safety concerns

4) Adverse Event Reporting & Non-Compliance

A. AE Grading: Intraoperative AEs per CTCAE v4.0; postoperative AEs per Clavien-Dindo Classifications.

a. AE Definition: Any unintended sign, symptom, or disease occurring within one week of protocol procedures, unrelated to expected physiological fluctuations. Data collection extends to 1 month post-op.
b. Permitted Co-Interventions: Antibiotics, plasma extenders, blood products, H2 blockers, PPIs, etc., without restriction.

B. Monitoring & Reporting: Bi-monthly reviews of enrollment, data quality, protocol/GCP compliance. IRB notified of SAEs, unexpected issues, or significant deviations. Immediate action and potential trial suspension if patient safety is at risk.

5) Study Suspension Criteria

A. Investigator judgment that continuation contradicts participant welfare, failure to meet enrollment targets, or emergence of concerning efficacy/safety data.

B. Upon suspension, the PI must notify the IRB and all investigators within two weeks; investigators must inform participants promptly.

12. Protections for Research Participants

1) Ethical Safeguards

All personnel will comply with the 2024 Declaration of Helsinki and ICH-GCP guidelines. Study begins only after IRB approval.

2) Informed Consent Process

A. Personnel obtaining consent: PI or delegated co-investigator

B. Consent provider: the participant

C. Waiting period between explanation and signing: 10 minutes to 2 days

D. Minimizing undue influence: Participation is voluntary; refusal incurs no penalty

E. Language used by investigators: Korean

F. Language understood by participants: Korean

G. Consent materials include study purpose, procedures, risks/benefits, contact information, data use, new findings disclosure, confidentiality protections, and a copy of the signed form.

3) Participant Compensation

In the event of trial-related AEs, appropriate medical care will be provided, and any hospitalization costs due to surgical complications will be minimized for the participant. Compensation is not provided for AEs arising from non-protocol treatments, unapproved procedures, participant negligence, or progression of underlying disease.

4) Privacy and Confidentiality

Personal identifiers will be coded and accessible only to the PI and designated staff. Documents (e.g., consent forms) will be kept under lock for three years post-study per local regulations, after which identifying data will be securely destroyed.

5) Vulnerable Populations

Not applicable

13. Handling and Disposal of Human-Derived Materials

Not applicable

14. References

1. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB (Oxford)*. Jun 2011;13(6):377-84. doi:10.1111/j.1477-2574.2011.00305.x

2. Hwang DW, Kim HJ, Lee JH, et al. Effect of Enhanced Recovery After Surgery program on pancreaticoduodenectomy: a randomized controlled trial. *J Hepatobiliary Pancreat Sci*. Aug 2019;26(8):360-369. doi:10.1002/jhbp.641

3. Koek SA, Ballal MS. Implementation of ERAS in pancreaticoduodenectomy in an Australian tertiary centre. *Pancreatology*. Jun 7 2023;doi:10.1016/j.pan.2023.06.004

4. Melloul E, Lassen K, Roulin D, et al. Guidelines for Perioperative Care for Pancreatoduodenectomy: Enhanced Recovery After Surgery (ERAS) Recommendations 2019. *World J Surg*. Jul 2020;44(7):2056-2084. doi:10.1007/s00268-020-05462-w

5. Noba L, Rodgers S, Doi L, Chandler C, Hariharan D, Yip V. Costs and clinical benefits of enhanced recovery after surgery (ERAS) in pancreaticoduodenectomy: an updated systematic review and meta-analysis. *J Cancer Res Clin Oncol*. Aug 2023;149(9):6639-6660. doi:10.1007/s00432-022-04508-x

6. Ergenc M, Karpuz S, Ergenc M, Yegen C. Enhanced recovery after pancreatic surgery: A prospective randomized controlled clinical trial. *J Surg Oncol*. Dec 2021;124(7):1070-1076. doi:10.1002/jso.26614

7. Fong ZV, Lwin TM, Aliaj A, Wang J, Clancy TE. Four-Day Robotic Whipple: Early Discharge after Robotic Pancreatoduodenectomy. *J Am Coll Surg*. Jun 1 2023;236(6):1172-1179. doi:10.1097/xcs.0000000000000560

8. Kuemmerli C, Tschuor C, Kasai M, et al. Impact of enhanced recovery protocols after pancreatoduodenectomy: meta-analysis. *Br J Surg*. Feb 24 2022;109(3):256-266. doi:10.1093/bjs/znab436

9. Koerner AS, Thomas AS, Chabot JA, Kluger MD, Sugahara KN, Schrope BA. Associations Between Patient Characteristics and Whipple Procedure Outcomes Before and After Implementation of an Enhanced Recovery After Surgery Protocol. *J Gastrointest Surg*. May 10 2023;doi:10.1007/s11605-023-05693-x

10. Ayala CI, Li AY, Lu A, et al. More Than an ERAS Pathway is Needed to Meet Target Length of Stay After Pancreaticoduodenectomy. *J Surg Res*. Feb 2022;270:195-202. doi:10.1016/j.jss.2021.08.034

11. Dai J, Jiang Y, Fu D. Reducing postoperative complications and improving clinical outcome: Enhanced recovery after surgery in pancreaticoduodenectomy - A retrospective cohort study. *Int J Surg*. Mar 2017;39:176-181. doi:10.1016/j.ijsu.2017.01.089

12. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. *World J Surg*. Mar 2019;43(3):659-695. doi:10.1007/s00268-018-4844-y

13. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery

after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *Br J Surg*. Sep 2014;101(10):1209-29. doi:10.1002/bjs.9582

14. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. Jul 2005;138(1):8-13. doi:10.1016/j.surg.2005.05.001

15. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM, Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg*. Jan 2013;216(1):1-14. doi:10.1016/j.jamcollsurg.2012.09.002

16. McMillan MT, Fisher WE, Van Buren G, 2nd, et al. The value of drains as a fistula mitigation strategy for pancreatoduodenectomy: something for everyone? Results of a randomized prospective multi-institutional study. *J Gastrointest Surg*. Jan 2015;19(1):21-30; discussion 30-1. doi:10.1007/s11605-014-2640-z

17. McMillan MT, Malleo G, Bassi C, et al. Multicenter, Prospective Trial of Selective Drain Management for Pancreatoduodenectomy Using Risk Stratification. *Ann Surg*. Jun 2017;265(6):1209-1218. doi:10.1097/SLA.0000000000001832

18. Beane JD, House MG, Ceppa EP, Dolejs SC, Pitt HA. Variation in Drain Management After Pancreatoduodenectomy: Early Versus Delayed Removal. *Ann Surg*. Apr 2019;269(4):718-724. doi:10.1097/SLA.0000000000002570

19. Kim SH, Hwang HK, Lee WJ, Kang CM. Comprehensive Complication Index or Clavien-Dindo Classification: Which is Better for Evaluating the Severity of Postoperative Complications Following Pancreatectomy? *World J Surg*. Mar 2021;45(3):849-856. doi:10.1007/s00268-020-05859-7

20. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. Aug 2009;250(2):187-96. doi:10.1097/SLA.0b013e3181b13ca2

21. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. Mar 2017;161(3):584-591. doi:10.1016/j.surg.2016.11.014