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Study Protocol for Preoperative Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to Main Pancreatic Duct: a multicenter randomized Clinical Trial

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Keywords:	Pancreatic surgery < SURGERY, Pancreatic disease < GASTROENTEROLOGY, Endocrine tumours < ONCOLOGY

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1 2 3 4 5 6	Roles and responsibilities: sponsor contact information	<u>#5b</u>	Name and contact information for the trial sponsor
7 8 9 10 11 12 13 14	Roles and responsibilities: sponsor and funder	<u>#5c</u>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
16 17 18 19 20 21 22 23	Roles and responsibilities: committees	<u>#5d</u>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
24 25 26 27 28 29	Background and rationale	<u>#6a</u>	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
30 31 32 33 34	Background and rationale: choice of comparators	<u>#6b</u>	Explanation for choice of comparators
35 36 37	Objectives	<u>#7</u>	Specific objectives or hypotheses
38 39 40 41 42 43 44	Trial design	<u>#8</u>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)
45 46 47 48 49 50	Methods: Participants, interventions, and outcomes		
51 52 53 54 55 56	Study setting	<u>#9</u>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
57 58 59 60	Eligibility criteria	<u>#10</u> For peer re	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Page 3 of 6

1			perform the interventions (eg, surgeons, psychotherapists)
2	Interventions:	#11a	Interventions for each group with sufficient detail to allow
5 4 5	description		replication, including how and when they will be administered
6 7	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated interventions for a
8 9 10	modifications		given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)
12	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention protocols, and any
13 14 15	adherance		procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
16 17	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
18 19 20	concomitant care		prohibited during the trial
21 22 23 24 25 26 27 28 29	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
30 31 32 33 34	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
35 36 37 38 39 40	Sample size	<u>#14</u>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
41 42 43	Recruitment	<u>#15</u>	Strategies for achieving adequate participant enrolment to reach target sample size
44 45	Methods: Assignment		
46 47	of interventions (for		
48 49	controlled trials)		
50 51	Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-
52 53 54 55 56 57 58 59	generation		generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
60	F	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2 3 4 5 6	Allocation concealmen mechanism	t <u>#16b</u>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4	BMJ Open: Tirst pub
7 8 9 10	Allocation: implementation	<u>#16c</u>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4	piisned as i Pr
11 12 13 14 15	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	iu. Ti solanijope nterted hv con
16 17 18 19 20 21	Blinding (masking): emergency unblinding	<u>#17b</u>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/Ag	wright includin
22 23 24	Methods: Data collection,				on 2 Apri En
25 26	management, and				seig
27	analysis			area	neme
28 29 30 31 32 33 34 35 36 37 28	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		ent Superieur (ABES) .
39 40 41 42 43	Data collection plan: retention	<u>#18b</u>	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A	en.omj.com/ or
44 45 46 47 48 49 50	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol		n June 13, zuza al A vilar tachnologias
50 51 52 53 54 55	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5	vgence בוטווטאַ
56 57 58 59 60	Statistics: additional analyses	<u>#20b</u> For peer re	Methods for any additional analyses (eg, subgroup and adjusted analyses) wiew only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	N/A	rapnique de i

1 2 3 4 5	Statistics: analysis population and missing data	<u>#20c</u>	Definition of analysis population relating to protocol non- adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A Open: first p
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8 9 10 11 12 13 14 15	Data monitoring: formal committee	<u>#21a</u>	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A Protected by cop
16 17 18 19 20 21	Data monitoring: interim analysis	<u>#21b</u>	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n-2023-078516 yright, includir N/A
22 23 24 25 26	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	on 2 April 2024 Enseign Ŋ/A uses rela N/A
27 28 29 30 31	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	. Downloaded fi ted to text and c N/A
32 33	Ethics and			rom Jata
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37 38 39	Research ethics approval	<u>#24</u>	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Al trainir
40 41 42 43 44 45 46	Protocol amendments	<u>#25</u>	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	mj.com/ on June 13 ıg, and similar tech N/A
47 48 49	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	nologies.
51	Consent or assent.	#26b	Additional consent provisions for collection and use of participant	N/A na
52 53 54	ancillary studies		data and biological specimens in ancillary studies, if applicable	Ce Bibli
55 56 57 58 59 60	Confidentiality	<u>#27</u> For peer re	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial eview only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5 5

Declaration of interests	<u>#28</u>	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Data access	<u>#29</u>	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5
Ancillary and post trial care	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A Protecte
Dissemination policy: trial results	<u>#31a</u>	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	₂d by copyright, inc
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Dissemination policy: reproducible research	<u>#31c</u>	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Enseigne uses relate
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Informed consent materials	<u>#32</u>	Model consent form and other related documentation given to participants and authorised surrogates	uperieur (۸ N/A data N/A
Biological specimens	<u>#33</u>	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	vBES) . n mining, Al trai N/Ang, Al trai
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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Primary Subject Heading :	Surgery
Secondary Subject Heading:	Surgery, Diabetes and endocrinology
Keywords:	Pancreatic surgery < SURGERY, Pancreatic disease < GASTROENTEROLOGY, Endocrine tumours < ONCOLOGY

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45 Abstract

46 <u>Introduction</u>

The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

55 <u>Methods and analysis</u>

This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple
tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in

58 the head and neck of the pancreas in proximity(≤ 2 mm) to the main pancreatic duct. Blocked

randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate measured by the International Study Group of Pancreatic Surgery (ISGPS) standard. Both interventions are performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the Chi-square test. The difference in secondary outcomes among the two groups will be analysed using appropriate tests.

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- *Ethics and dissemination*
- 69 The study was approved by the Peking Union Medical College Hospital Institutional Review
 70 Board (K23C0195). Results of the study will be published in an international peer-reviewed
 71 journal.
- 72 <u>Trial registration number</u>
- 73 ClinicalTrials. gov Registry (NCT05523778).
- 74 Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic fistula
 - 75 <u>Article Summary</u>
- 76 Strengths and limitations of this study
 - 77 > A prospective multicenter clinical design to assess the efficacy and safety of a preventive
 78 intervention in improving the outcome of enucleation surgery.
- 79 > Recruiting patients from multiple tertiary medical centers across China.
- 80 > Local online communication tool exploited to promote interactions between investigators
 81 and patients

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82 > The lack of blinding of the patients, surgeons, data collectors, and data analysts is the
83 limitation of the study.

84 Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with
an estimated incidence of 1–4 per million per year [1, 2] They are insulin-secreting tumors
that cause common clinical features including neuroglycopenia and autonomic nervous
system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management
remains the only curative modality for 90% of benign, localized insulinomas[4, 6].

According to several guidelines including the National Comprehensive Cancer Network
(NCCN) and the European Neuroendocrine Tumor Society (ENETs)[7, 8], enucleation(EN),
a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine
insufficiency, should be considered as the first-line surgical approach for exophytic and
peripheral insulinomas[9].

However, in cases of endophytic insulinomas or tumors in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large PNETS.[12] In contrast, performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly rate of post-operative morbidity, especially postoperative pancreatic elevated

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fistula(POPF). Lu et.al compared post-operative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors located ≤ 3 mm from the MPD [14]. Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumors located at less than or equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD < 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD. POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field thus preventing intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients and were single-armed studies. Based on the knowledge and shortcomings on this topic, our team has collected 18 patients undergoing preoperative stenting in our center for 5 years. We retrospectively analyzed the risk factor of postoperative complications, especially POPF, and discovered

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127	that the distance from insulinoma to MPD \leq 2 mm was an independent risk factor for POPF
128	(OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced
129	the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs
130	71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the
131	efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck
132	of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic
133	Surgery (www.evidencemap.surgery), this is the first trial of its kind[23].
134	Methods and analysis
135	Study setting
136	This is a multicenter, double-arm, prospective, randomized trial in five high-volume medical
137	centers in China. Experienced surgeons will determine the eligibility of their patients and
138	obtain informed consent forms. Eligible patients with insulinoma in proximity to the MPD
139	(\leq 2mm) will be allocated randomly into two groups: Stented EN group, where the
140	pancreatic duct stents are placed in patients by endoscopist within 24 hours before the
141	enucleation surgery, and Direct EN group, where patients receive direct enucleation
142	surgery. An overview of the protocol is shown in Figure 1. The study started in February
143	2023 and was planned to finish patient recruitment in December 2025.
144	➢ Endpoints
145	Primary endpoint: Rate of POPF within 3 months after EN.
146	Secondary endpoints:
147	1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks
148	after EN

2) Operation time

3) Intraoperative blood loss

10) Total cost of hospitalization

Patients eligibility

Randomization

Definition

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4) Rate of postoperative abdominal infection within 3 weeks after EN

6) Rate of postoperative lung infection within 3 weeks after EN

8) Rate of postoperative dyspepsia within 6 months after EN

adverse events are defined as grade 3 or higher in CTCAE.

Inclusion and exclusion criteria are shown in Box 1

9) Rate of postoperative hyperglycemia within 6 months after EN

5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN

7) Rate of postoperative delayed gastric emptying within 3 weeks after EN

In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by

the international pancreatic surgery research group (ISGPS) [24-26]. Pancreatitis,

abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated

based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe

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Randomization will be initiated by authorized investigators of the trial after checking the

informed consent and the inclusion and exclusion criteria. Each eligible patient will be

allocated an individual code/randomization number, which has to be recorded in case

report form (CRF). Blocked randomization (blocked number=4) for each center will be

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performed using SAS Studio by the study assistant prior to the beginning of enrollment.
After randomization, surgeons in all centers who enroll the patient will be informed of the
intervention assignment.

174 ➤ Blindness

In accordance with recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two condition the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records which are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts unviable. Recognizing the critical importance of blinding in assessing primary and secondary endpoints, especially those related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with

3 4 5	193	objective clinical data which can be provided to independent assessors with blindness of
6 7	194	allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of
8 9 10	195	primary and secondary outcomes while concurrently insulating the operating surgeon from
11 12 13	196	subjective judgment regarding clinical endpoints. Emergency unblinding is not deemed
14 15	197	necessary.
16 17 18	198	 Study interventions
19 20 21	199	After baseline visit and admission, eligible participants are randomized to the stented EN
22 23	200	group or the direct EN group, as shown in Figure 1.
24 25 26	201	Preoperative MPD stenting
27 28	202	The preoperative pancreatic duct stent was regarded as a possible effective method to
29 30 31 32 33 34	203	prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours
	204	before the enucleation endoscopically. The stent length should span the site of the tumor.
35 36	205	The length and the diameter of the stent used should be recorded in CRF. The stent was
37 38 39	206	removed by duodenoscopy about three months after surgery. Endoscopic stent placement
40 41 42	207	and removal represents a common procedure at the Endoscopic Center of Peking Union
43 44	208	Medical College Hospital and other centers and will be carried out by experienced
45 46 47	209	endoscopists (minimum of 50 procedures) for the study. Any adverse events should be
48 49	210	recorded in CRF including stent-related pancreatitis. Blood amylase is tested 2-4 hours
50 51 52	211	after stenting before enucleation to discover potential stenting-related acute pancreatitis.
53 54 55	212	■ Enucleation
56 57	213	During the surgery, intraoperative ultrasound will be performed to evaluate the location of
58 59 60	214	the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule

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> covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon sutures the lesion and suspends it, and then the insulinoma is dissected from the normal pancreatic tissue. Dissection was performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens are regularly investigated to identify benign insulinomas. The operative field should be carefully examined and MPD disruption should be repaired immediately once detected. The prophylactic abdominal drainage tube is applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume should be recorded in CRF.

Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood was routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the drainage tube has not been removed at the time of discharge, the patient would be instructed to record the daily drainage until extubation in the outpatient setting.

233 ■ Follow-up

For the first three months after discharge, patients should maintain a regular follow-up
session for every two weeks through outpatient or telephone. The following information
should be collected during each follow-up: basic information and general condition of the

3 4 5	237	patient, whether the patient has been extubated (if not extubated, record the recent					
6 7	238	drainage condition), recent medical interventions, and possible manifestations of					
9 10	239	dyspepsia or hyperglycemia. Laboratory tests and imaging examinations will be done at					
11 12 13	240	the surgeon's discretion.					
14 15 16	241	 Statistical methods 					
17 18	242	Hypothesis					
19 20 21	243	 Null hypothesis 					
22 23	244	The rate of POPF in patients who undergo MPD stent placement before enucleation					
24 25 26	245	is not less than that of patients who undergo enucleation directly.					
27 28 29	246	Alternative hypothesis					
30 31	247	The rate of POPF in patients who undergo MPD stent placement before enucleation					
32 33 34	248	is less than that of patients who undergo enucleation directly.					
35 36 27	249	 Sample size calculation 					
38 39	250	In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the					
40 41 42	251	MPD who underwent enucleation were included, of which 16 had stent placement and 28					
43 44	252	had no stent placement, ands, 38 evaluable patients per group will provide 85% power to					
45 46 47	253	reject the null hypothesis in a Z test(unpooled) for superiority at a one-sided significance					
48 49 50	254	level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically					
50 51 52	255	relevant difference. Therefore, 78 patients in total are to be recruited in the study					
53 54 55	256	considering possible dropout.					
56 57 58 59 60	257	Statistical analysis					

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> The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% Cls. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square tests, Fisher's exact tests, etc.).

267 Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board(approval number K23C0195) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki[28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal.

276 > Patient and public involvement

277 Throughout the study, a study account based on a local online communication tool278 (WeChat) will be established to receive any suggestions and consultations from patients

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3	070	
4	279	involved and information about the study will be updated for all patients who subscribed to
6		
7	280	the study account.
8		
9	281	
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11 12	282	Discussion
12	202	
14	000	
15	283	Generally, enucleation is preferred over other operation approaches in treating insulinomas,
16		
17	284	as it circumvents complicated reconstructions and possible subsequent complications.
18		
19 20	285	However, POPF is common in the enucleation of insulinomas that are in proximal to MPD,
20		
22	286	which limits its clinical application. In this clinical trial, we aim to demonstrate the safety
23	200	which innes its clinical application. In this clinical that, we aim to demonstrate the safety
24		
25	287	and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies
26		
27	288	have shown promising effects of MPD stent in prevention of POPF but with limited evidence.
20		
30	289	In this study, we aim to include patients who are prone to suffer from POPF to validate the
31		
32	200	efficacy of MPD stept. In our previous research, we demonstrated the distance from
33	230	encacy of wird stent. In our previous research, we demonstrated the distance norm
34 35		
36	291	insulinoma to MPD ≤ 2 mm was an independent risk factor for POPF. Therefore, it is a
37		
38	292	reasonable and feasible choice to confine patients whose tumors are "deep" in our ongoing
39		
40	293	trial. Preoperative MPD stent placement, as an extra intervention procedure for treating
41		
42 43	201	insulinoma is still a vacue yet practical technique in the prevention of POPE. Thus, the
44	234	insumorna, is suit a vague yet practical technique in the prevention of 1 of 1. Thus, the
45		
46	295	conduction of this clinical trial in a randomized controlled way is under the general ethical
47		
48	296	principle of clinical equipoise according to our present knowledge. In this way, the result of
49 50		
50	297	this multicenter, prospective, randomized control clinical trial can offer substantial
52		
53	208	information on the feasibility of this approach, and thus hopefully widen the indication of
54	200	mormation on the reasibility of this approach, and thus hopefully widen the indication of
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סט 57	299	enucleation and partially alter the treatment pathway of insulinoma.
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Author Contributions

302	Contributors GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR
303	drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision
304	of the manuscript. XQ obtained the funding for this study. All the authors read and approved
305	the final manuscript.
306	Funding The trial will be supported by a grant from the National High Level Hospital Clinical
307	Research Funding(2022-PUMCH-A-050).
308	<i>Disclaimer</i> The funder will have no role in the conduct or analysis of the trial.
309	<u>Competing interests</u> None declared.
310	
311	Total word count: 2466
312	Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated
313	hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US,
314	ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.
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40	102	Pay 1 Inclusion and evaluation criteria
41	403	
42 43		Inclusion Criteria
44		> Age 18-75 years
45 46		The clinical qualitative diagnosis of insulinoma was clear;
47		The localization diagnosis was clear, and it was determined that the tumor was
48 49		single, located in the head and neck;
50		The distance between the tumor and the main pancreatic duct was determined to
51		h = 1 $h = 1$ $h =$
52 53		Truly informed and voluntarily participate in this study, with written informed
54		· muy morned and voluntarily participate in this study, with written informed
55 56		consent.
57		Exclusion Criteria
58		Maximum diameter of the tumor >2cm proved pathologically
59 60		 Severe cardiopulmonary complications

2		
3 ⊿		Combined with other known tumor diseases
5		Invasive insulinoma or insulinoma with suspicious metastasis
6		 Previous upper abdominal surgery history
7 8		 Refusal or inability to cooperate in the study.
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		name of intended registry
Trial registration:	<u>#2b</u>	All items from the World Health Organization Trial
data set		Registration Data Set
Protocol version	<u>#3</u>	Date and version identifier
Funding	<u>#4</u>	Sources and types of financial, material, and other
		support
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors
responsibilities:		
contributorship		
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor
responsibilities:		
sponsor contact		
information		
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study
responsibilities:		design; collection, management, analysis, and
sponsor and funder		interpretation of data; writing of the report; and the
		decision to submit the report for publication, including
		whether they will have ultimate authority over any of
		these activities
Roles and	<u>#5d</u>	Composition, roles, and responsibilities of the
responsibilities:		coordinating centre, steering committee, endpoint
committees		adjudication committee, data management team, and
		other individuals or groups overseeing the trial, if

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		applicable (see Item 21a for data monitoring committee)
Introduction		
Background and	<u>#6a</u>	Description of research question and justification for
rationale		undertaking the trial, including summary of relevant
		studies (published and unpublished) examining
		benefits and harms for each intervention
Background and	<u>#6b</u>	Explanation for choice of comparators
rationale: choice of		
comparators		
Objectives	<u>#7</u>	Specific objectives or hypotheses
Trial design	<u>#8</u>	Description of trial design including type of trial (eg,
		parallel group, crossover, factorial, single group),
		allocation ratio, and framework (eg, superiority,
		equivalence, non-inferiority, exploratory)
Methods:		
Participants,		
interventions, and		
outcomes		
Study setting	<u>#9</u>	Description of study settings (eg, community clinic,
		academic hospital) and list of countries where data
		will be collected. Reference to where list of study sites
		can be obtained
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1 2	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If
3 4			applicable, eligibility criteria for study centres and
5 6 7			individuals who will perform the interventions (eg,
, 8 9			surgeons, psychotherapists)
10 11 12	Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to
13 14	description		allow replication, including how and when they will be
15 16 17			administered
18 19 20	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated
20 21 22	modifications		interventions for a given trial participant (eg, drug
23 24			dose change in response to harms, participant
25 26 27			request, or improving / worsening disease)
28 29	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention
30 31 32	adherance		protocols, and any procedures for monitoring
33 34 35			adherence (eg, drug tablet return; laboratory tests)
36 37	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are
38 39 40	concomitant care		permitted or prohibited during the trial
41 42	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including
43 44 45			the specific measurement variable (eg, systolic blood
46 47			pressure), analysis metric (eg, change from baseline,
48 49			final value, time to event), method of aggregation (eg,
50 51 52			median, proportion), and time point for each outcome.
52 53 54			Explanation of the clinical relevance of chosen
55 56			efficacy and harm outcomes is strongly recommended
57 58			
60	I	or peer re	eview only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including
3 4			any run-ins and washouts), assessments, and visits
5 6 7			for participants. A schematic diagram is highly
7 8 9 10			recommended (see Figure)
11 12	Sample size	<u>#14</u>	Estimated number of participants needed to achieve
13 14			study objectives and how it was determined, including
15 16 17			clinical and statistical assumptions supporting any
18 19 20			sample size calculations
21 22	Recruitment	<u>#15</u>	Strategies for achieving adequate participant
23 24 25			enrolment to reach target sample size
26 27	Methods:		
28 29 30	Assignment of		
50			
31 32	interventions (for		
31 32 33 34 35	interventions (for controlled trials)		
31 32 33 34 35 36 37	interventions (for controlled trials) Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,
31 32 33 34 35 36 37 38 39 40	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any
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 31 32 33 34 35 36 37 38 39 40 41 42 43 44 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 40 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol
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31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58	interventions (for controlled trials) Allocation: sequence generation Allocation concealment mechanism	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to

1 2			conceal the sequence until interventions are assigned
3 4	Allocation:	<u>#16c</u>	Who will generate the allocation sequence, who will
5 6 7	implementation		enrol participants, and who will assign participants to
7 8 9 10			interventions
11 12	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions
13 14			(eg, trial participants, care providers, outcome
15 16 17			assessors, data analysts), and how
18 19 20	Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is
21 22	emergency		permissible, and procedure for revealing a
23 24 25	unblinding		participant's allocated intervention during the trial
26 27	Methods: Data		
28 29 30	collection,		
31	management and		
32	manayement, anu		
32 33 34 35	analysis		
32 33 34 35 36 37	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome,
32 33 34 35 36 37 38 39	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related
32 33 34 35 36 37 38 39 40 41 42	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate
32 33 34 35 36 37 38 39 40 41 42 43 44	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a
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32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity,
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32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53	analysis Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	analysis Data collection plan Data collection plan:	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Plans to promote participant retention and complete
32 33 34 35 36 37 38 30 41 42 43 445 46 47 48 951 52 53 54 55 55 57 55 57 55	analysis Data collection plan Data collection plan: retention	<u>#18a</u>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Plans to promote participant retention and complete follow-up, including list of any outcome data to be

N/A

1			collected for participants who discontinue or deviate
2 3 4			from intervention protocols
5 6	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,
7 8 9			including any related processes to promote data
10 11			quality (eg, double data entry; range checks for data
12 13			values). Reference to where details of data
14 15			management procedures can be found, if not in the
16 17 18			protocol
19 20 21	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and
21 22 23			secondary outcomes. Reference to where other
24 25			details of the statistical analysis plan can be found, if
26 27 28			not in the protocol
20 29 30	Statistics: additional	#205	Mathada far any additional analyses (og. subgroup
31 32		#200	and adjusted analyses (eg, subgroup
33 34	analyses		and adjusted analyses)
35 36 27	Statistics: analysis	<u>#20c</u>	Definition of analysis population relating to protocol
37 38 39	population and		non-adherence (eg, as randomised analysis), and any
40 41	missing data		statistical methods to handle missing data (eg,
42 43			multiple imputation)
44 45 46 47	Methods: Monitoring		
48 49	Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);
50 51 52	formal committee		summary of its role and reporting structure; statement
52 53 54			of whether it is independent from the sponsor and
55 56			competing interests; and reference to where further
57 58			details about its charter can be found, if not in the
59 60	F	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Page 2	8 of 3	29	
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1			protocol. Alternatively, an explanation of why a DMC
2 3			is not needed
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6 7	Data monitoring:	<u>#21b</u>	Description of any interim analyses and stopping
8 9	interim analysis		guidelines, including who will have access to these
10 11			interim results and make the final decision to
12 13			terminate the trial
14 15			
16 17	Harms	<u>#22</u>	Plans for collecting, assessing, reporting, and
18 19			managing solicited and spontaneously reported
20 21			adverse events and other unintended effects of trial
22 23			interventions or trial conduct
24 25			
25 26 27	Auditing	<u>#23</u>	Frequency and procedures for auditing trial conduct, if
28 29			any, and whether the process will be independent
30 31			from investigators and the sponsor
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33 34	Ethics and		
35 36	dissemination		
37 38	Research ethics	#24	Plans for seeking research ethics committee /
39 40		<u> <i>π</i></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u> <u></u>	Thans for seeking research ethics committee /
41 42	approval		institutional review board (REC / IRB) approval
43 44	Protocol	<u>#25</u>	Plans for communicating important protocol
45 46 47	amendments		modifications (eg, changes to eligibility criteria,
48 49			outcomes, analyses) to relevant parties (eg,
50 51			investigators REC / IRBs trial participants trial
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55 54			registries, journals, regulators)
55 56 57	Consent or assent	<u>#26a</u>	Who will obtain informed consent or assent from
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		potential trial participants or authorised surrogates,
		and how (see Item 32)
Consent or assent:	<u>#26b</u>	Additional consent provisions for collection and use of
ancillary studies		participant data and biological specimens in ancillary
		studies, if applicable
Confidentiality	<u>#27</u>	How personal information about potential and enrolled
		participants will be collected, shared, and maintained
		in order to protect confidentiality before, during, and
		after the trial
Declaration of	<u>#28</u>	Financial and other competing interests for principal
interests		investigators for the overall trial and each study site
Data access	<u>#29</u>	Statement of who will have access to the final trial
		dataset, and disclosure of contractual agreements
		that limit such access for investigators
Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and
trial care		for compensation to those who suffer harm from trial
		participation
Dissemination	<u>#31a</u>	Plans for investigators and sponsor to communicate
policy: trial results		trial results to participants, healthcare professionals,
		the public, and other relevant groups (eg, via
		publication, reporting in results databases, or other
		data sharing arrangements), including any publication
		restrictions
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1	Dissemination	<u>#31b</u>	Authorship eligibility guidelines and any intended use	8MJ 7 0
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17 18 10	Informed consent	<u>#32</u>	Model consent form and other related documentation	See suppleme
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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

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Secondary Subject Heading:	Surgery, Diabetes and endocrinology
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45 Abstract

46 <u>Introduction</u>

The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

55 <u>Methods and analysis</u>

This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple
tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in

58 the head and neck of the pancreas in $proximity(\leq 2mm)$ to the main pancreatic duct. Blocked

randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate measured by the International Study Group of Pancreatic Surgery (ISGPS) standard. Both interventions are performed in an inpatient setting and regular follow-up will be performed. The primary outcome (POPF rate) will be tested for superiority with the Chi-square test. The difference in secondary outcomes among the two groups will be analysed using appropriate tests.

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- *<u>Ethics and dissemination</u>*
- 69 The study was approved by the Peking Union Medical College Hospital Institutional Review
 70 Board (K23C0195). Results of the study will be published in an international peer-reviewed
 71 journal.
- 72 <u>Trial registration number</u>
 - 73 ClinicalTrials. gov Registry (NCT05523778).
- 74 Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic fistula
 - 75 <u>Article Summary</u>
- 76 Strengths and limitations of this study
 - 77 > A prospective multicenter clinical design to assess the efficacy and safety of a preventive
 78 intervention in improving the outcome of enucleation surgery.
- 79 > Recruiting patients from multiple tertiary medical centers across China.
- 80 > Local online communication tool exploited to promote interactions between investigators
 81 and patients

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82	\triangleright	The lack of blinding of the patients, surgeons, data collectors, and data analysts is the
83		limitation of the study.

84 Introduction

Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with
an estimated incidence of 1–4 per million per year [1, 2] They are insulin-secreting tumors
that cause common clinical features including neuroglycopenia and autonomic nervous
system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management
remains the only curative modality for 90% of benign, localized insulinomas[4, 6].

According to several guidelines including the National Comprehensive Cancer Network
(NCCN) and the European Neuroendocrine Tumor Society (ENETs)[7, 8], enucleation(EN),
a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine
insufficiency, should be considered as the first-line surgical approach for exophytic and
peripheral insulinomas[9].

However, in cases of endophytic insulinomas or tumors in proximity to the main pancreatic duct (MPD), the optimal choice of surgical intervention is controversial. Standard pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue, which can lead to long-term consequences including exocrine and endocrine pancreatic insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR) was alternatively recommended for the resection of large PNETS.[12] In contrast, performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD still baffles many surgeons as several retrospective researches suggested a significantly elevated rate of post-operative morbidity, especially postoperative pancreatic

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fistula(POPF). Lu et.al compared post-operative morbidity between PD and EN, indicating a significant difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors located ≤ 3 mm from the MPD [14]. Another study involving 52 patients who underwent EN also demonstrated a high POPF rate of 60% in the group of tumors located at less than or equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD < 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive measures in EN that decrease the POPF rate would encourage the implementation of EN thus improving the long-term benefits for patients with insulinomas in proximity to the MPD. POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative stenting is believed to prevent the MPD injury in that it not only helps to identify the location of MPD in the surgical field thus preventing intraoperative damage but also decompresses pancreatic duct by reducing pancreatic juice leakage from the resection plane and providing support to the duct when stricture develops. Pertinent clinical evidence involving stenting and EN is still lacking. Some researchers reported the usage of preoperative stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and safety of the technique, most of these researches involved a limited number of patients and were single-armed studies. Based on the knowledge and shortcomings on this topic, our team has collected 18 patients undergoing preoperative stenting in our center for 5 years. We retrospectively analyzed the risk factor of postoperative complications, especially POPF, and discovered

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127	that the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF
128	(OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced
129	the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs
130	71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the
131	efficacy and safety of preoperative stenting before EN of insulinoma in the head and neck
132	of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic
133	Surgery (www.evidencemap.surgery), this is the first trial of its kind[23].
134	Methods and analysis
135	Study setting
136	This is a multicenter, double-arm, prospective, randomized trial in five high-volume medical
137	centers in China. Experienced surgeons will determine the eligibility of their patients and
138	obtain informed consent forms. (see Supplementary Materials) Eligible patients with
139	insulinoma in proximity to the MPD (\leq 2mm) will be allocated randomly into two groups:
140	Stented EN group, where the pancreatic duct stents are placed in patients by endoscopist
141	within 24 hours before the enucleation surgery, and Direct EN group, where patients
142	receive direct enucleation surgery. An overview of the protocol is shown in Figure 1. The
143	study started in February 2023 and was planned to finish patient recruitment in December
144	2025.
145	> Endpoints
146	Primary endpoint: Rate of POPF within 3 months after EN.

147 Secondary endpoints:

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2		
3		
4	148	1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks
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6	140	offer EN
7	149	
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9	150	2) Operation time
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11	454	
12	151	3) Intraoperative blood loss
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14	152	4) Rate of postoperative abdominal infection within 3 weeks after EN
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16		
17	153	5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN
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19	154	6) Rate of postoperative lung infection within 3 weeks after EN
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22	155	7) Rate of postoperative delayed gastric emptying within 3 weeks after EN
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24	156	9) Data of postanerative dypanois within 6 months ofter EN
25	150	o) Rate of postoperative dyspepsia within o months after EN
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2/	157	9) Rate of postoperative hyperglycemia within 6 months after EN
28		
29	450	
50 21	158	10) Total cost of hospitalization
21 22		
22	159	> Definition
31		
35	400	
36	160	In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by
37		
38	161	the international pancreatic surgery research group (ISGPS) [24-26]. Pancreatitis,
39		
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41	162	abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated
42		
43	163	based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe
44		
45		
46	164	adverse events are defined as grade 3 or higher in CTCAE.
47		
48	165	Patients eligibility
49	100	
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51	166	Inclusion and exclusion criteria are shown in Box 1
52		
53	167	Dandomization
54	107	
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56	168	Randomization will be initiated by authorized investigators of the trial after checking the
57		
58	400	Sufference of a supervised state (a short-second state) (1997) (1997) (1997) (1997) (1997)
59	169	informed consent and the inclusion and exclusion criteria. Each eligible patient will be
60		

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170 allocated an individual code/randomization number, which has to be recorded in case 171 report form (CRF). Blocked randomization (blocked number=4) for each center will be 172 performed using SAS Studio by the study assistant prior to the beginning of enrollment. 173 After randomization, surgeons in all centers who enroll the patient will be informed of the 174 intervention assignment.

Blindness

In accordance with recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two condition the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records which are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts unviable. Recognizing the critical importance of blinding in assessing primary and secondary endpoints, especially those

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related to complications, outcome assessors are kept blinded to participant group allocation. Based on our protocol, the assessment of endpoints is directly linked with objective clinical data which can be provided to independent assessors with blindness of allocation. This strategy plays a pivotal role in reducing potential bias in the assessment of primary and secondary outcomes while concurrently insulating the operating surgeon from subjective judgment regarding clinical endpoints. Emergency unblinding is not deemed necessary.

199 > Study interventions

After baseline visit and admission, eligible participants are randomized to the stented EN
group or the direct EN group, as shown in Figure 1.

202 Preoperative MPD stenting

The preoperative pancreatic duct stent was regarded as a possible effective method to prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours before the enucleation endoscopically. The stent length should span the site of the tumor. The length and the diameter of the stent used should be recorded in CRF. The stent was removed by duodenoscopy about three months after surgery. Endoscopic stent placement and removal represents a common procedure at the Endoscopic Center of Peking Union Medical College Hospital and other centers and will be carried out by experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events should be recorded in CRF including stent-related pancreatitis. Blood amylase is tested 2-4 hours after stenting before enucleation to discover potential stenting-related acute pancreatitis.

213 Enucleation

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> During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon sutures the lesion and suspends it, and then the insulinoma is dissected from the normal pancreatic tissue. Dissection was performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens are regularly investigated to identify benign insulinomas. The operative field should be carefully examined and MPD disruption should be repaired immediately once detected. The prophylactic abdominal drainage tube is applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume should be recorded in CRF.

225 ■ Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood was routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the drainage tube has not been removed at the time of discharge, the patient would be instructed to record the daily drainage until extubation in the outpatient setting.

Follow-up

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235	For the first three months after discharge, patients should maintain a regular follow-up
236	session for every two weeks through outpatient or telephone. The following information
237	should be collected during each follow-up: basic information and general condition of the
238	patient, whether the patient has been extubated (if not extubated, record the recent
239	drainage condition), recent medical interventions, and possible manifestations of
240	dyspepsia or hyperglycemia. Laboratory tests and imaging examinations will be done at
241	the surgeon's discretion. Normally, CT or MRI scans will be performed routinely at 3
242	months postoperatively, just before stent removal, and then again 3 months after the stent
243	removal.
244	 Statistical methods
245	Hypothesis
246	Null hypothesis
247	The rate of POPF in patients who undergo MPD stent placement before enucleation
248	is not less than that of patients who undergo enucleation directly.
249	Alternative hypothesis
250	The rate of POPF in patients who undergo MPD stent placement before enucleation
251	is less than that of patients who undergo enucleation directly.
252	Sample size calculation
253	In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the
254	MPD who underwent enucleation were included, of which 16 had stent placement and 28
255	had no stent placement, ands, 38 evaluable patients per group will provide 85% power to
256	reject the null hypothesis in a Z test(unpooled) for superiority at a one-sided significance

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level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically
relevant difference. Therefore, 78 patients in total are to be recruited in the study
considering possible dropout.

Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% Cls. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square

269 tests, Fisher's exact tests, etc.).

270 Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by the Peking Union Medical College Hospital Institutional Review Board(approval number K23C0195) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki[28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal.

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In response to the submission and approval of our protocol, several modifications have been incorporated into the study design, all of which have undergone thorough scrutiny and received approval from our ethics committee. Firstly, a new timepoint at postoperative day 7 (pod7) has been added for the measurement of amylase levels, leveraging the existing practice of routinely measuring amylase levels for all patients at this timepoint. Secondly, we have introduced an exclusion criterion based on the maximum diameter of the tumor (>2cm), a feasible addition given that no enrolled patients before this change meet the exclusion criteria. Thirdly, a significant refinement involves blinding outcome assessors, a practicable adjustment as assessors can re-evaluate outcomes solely based on the information recorded in the case report form (CRF). Lastly, we have clarified that the primary outcome measurement will occur at 90 days postoperatively, enhancing precision in reporting the study's findings. These modifications aim to strengthen the study's scientific integrity, participant safety, and overall methodological rigor. Patient and public involvement Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients involved and information about the study will be updated for all patients who subscribed to the study account. Discussion Generally, enucleation is preferred over other operation approaches in treating insulinomas,

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as it circumvents complicated reconstructions and possible subsequent complications.

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> However, POPF is common in the enucleation of insulinomas that are in proximal to MPD, which limits its clinical application. In this clinical trial, we aim to demonstrate the safety and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies have shown promising effects of MPD stent in prevention of POPF but with limited evidence. In this study, we aim to include patients who are prone to suffer from POPF to validate the efficacy of MPD stent. In our previous research, we demonstrated the distance from insulinoma to MPD ≤2 mm was an independent risk factor for POPF. Therefore, it is a reasonable and feasible choice to confine patients whose tumors are "deep" in our ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, the conduction of this clinical trial in a randomized controlled way is under the general ethical principle of clinical equipoise according to our present knowledge. In this way, the result of this multicenter, prospective, randomized control clinical trial can offer substantial information on the feasibility of this approach, and thus hopefully widen the indication of enucleation and partially alter the treatment pathway of insulinoma.

317 Author Contributions

318 <u>*Contributors*</u> GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR 319 drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision 320 of the manuscript. XQ obtained the funding for this study. All the authors read and approved 321 the final manuscript.

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4	323	Researc	n Funding(2022-PUMCH-A-050).
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7	324	Disclaim	<u>ner</u> The funder will have no role in the conduct or analysis of the trial.
8			
9	325	Compet	<i>ting interests</i> None declared.
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17	328	Figure 1	1 Flow chart of the study FBG fasting blood glucose. HbA1c glycosylated
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20	329	hemoglo	bbin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US,
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22	330	ultrasou	nd; DM, diabetes mellitus; ASA American Society of Anesthesiology.
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24		
25	419	Box 1 Inclusion and exclusion criteria
26		
27		Inclusion Criteria
28		Age 18-75 years
29		
30		The clinical qualitative diagnosis of insulinoma was clear;
31		> The localization diagnosis was clear, and it was determined that the tumor was
32 22		
37		single, located in the head and heck;
35		> The distance between the tumor and the main pancreatic duct was determined to
36		$h_0 < 2mm$ by propagative imaging (enhanced CT, MDL etc.):
37		be $\leq 2 \min by preoperative imaging (emanced C1, MRI, etc.),$
38		> Truly informed and voluntarily participate in this study, with written informed
39		consent
40		consent.
41		Exclusion Criteria
42		> Maximum diameter of the tumor >2cm proved pathologically
43		
44		Severe cardiopulmonary complications
45		Combined with other known tumor diseases
46		
47		Invasive insulinoma or insulinoma with suspicious metastasis
48		Previous upper abdominal surgery history
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50		Refusal or inability to cooperate in the study
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informed consent form
Preoperative Pancreatic Stents
Placement Before the Enucleation of
Insulinoma Located in the Head and
Neck of the Pancreas in Proximity to
the Main Pancreatic Duct
C
Peking Union Medical College Hospital,
Chinese Academy of Medical Sciences
Qiang Xu
V3.0
2022/12/30

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Dear Subject:

We would like to invite you to participate in a clinical study entitled "A Randomized Controlled Study of Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct ".

Before you decide whether to consent to participate, please read this informed consent form carefully and ask the investigators questions about your concerns. You may also ask your family, friends, or others. Once you have decided to participate in the study, you will be asked to sign this informed consent form.

1. Research Background

Insulinoma is the most common type of functional pancreatic endocrine tumors, which is characterized by uncontrolled excessive insulin secretion. Its main treatment is surgical resection. 90% of patients with insulinoma can be cured by surgical treatment. We found that for insulinomas located in the pancreatic head and neck near the main pancreatic duct, enucleation is prone to cause main pancreatic duct injury, which increases the risk of postoperative pancreatic fistula and other serious complications. Therefore, pancreaticoduodenectomy is recommended, but it requires combined resection of part of the stomach, duodenum, common bile duct and gallbladder, and there is a high risk of postoperative pancreatic exocrine insufficiency. In contrast, enucleation still has the advantages of less trauma and low incidence of long-term postoperative pancreatic secretion insufficiency, which is of great help to improve the long-term quality of life of patients after surgery. At present, the surgical management of this type of tumor is still inconclusive in the world, and many large pancreatic centers are still conducting clinical studies on enucleation. Studies have shown that preoperative placement of pancreatic duct stents followed by enucleation can reduce the incidence of postoperative pancreatic fistula and increase the long-term postoperative benefits, but the placement of pancreatic duct stents may cause stent-related adverse events. However, the placement of pancreatic stent may cause stent-related adverse events. However, there is no high-level clinical study to demonstrate its advantages and disadvantages. Therefore, the aim of this study is to investigate the safety and efficacy of preoperative pancreatic stent placement in patients with insulinoma in the pancreatic head and neck near the main pancreatic duct through a multi-center randomized controlled trial, so as to provide evidence-based medical evidence for standardized treatment of insulinoma and thus to change the current treatment guidelines.

This study was approved by the Peking Union Medical College Hospital Ethics Committee.

2. What was the purpose of this clinical study?

To compare the clinical efficacy, safety and efficacy between direct enucleation and preoperative placement of pancreatic stent followed by enucleation for insulinoma near the main pancreatic duct in the head and neck of the pancreas, and to evaluate the application value of the former surgical treatment strategy.

3. Methods: Study

This study was an intervention study. Participants were divided into two groups: experimental

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group and control group. Enrollment in the two groups is 1:1, grouping will be random (like a lottery), and neither you nor the investigator can choose in advance which group to participate in. The study was unblinded, meaning that after randomization, you, the investigator, and the clinician knew which group you had been assigned to. The study had an anticipated enrollment of 78 patients nationwide.

4. Study PROCESS

 Before commencing any research related activities, you will first need to sign this informed consent form.

During the screening period, the researcher will ask and collect your personal information, previous diagnosis and treatment, your combined medications, comorbidities, and order your blood routine, liver function, renal function, pancreatic function, fasting blood glucose, insulin, C-peptide, abdominal and pelvic enhanced CT, MRI and other examinations. We will determine whether you meet the inclusion criteria through your current clinical symptoms, performance, and examination results.

If you meet the eligibility criteria, study treatment will be initiated, and you will be randomly assigned to either an experimental group (placement of a pancreatic duct stent before enucleation) or a control group (enucleation alone). You will then proceed to endoscopic stent placement and surgery according to standard protocols.

During your hospitalization, we will collect your laboratory test results, surgery-related information, and recovery, which do not require your additional cooperation. If you are assigned to the experimental group, you will be scheduled to undergo ERCP-guided pancreatic duct stenting approximately 1 day before the procedure, which is in accordance with the usual practice of our hospital.

After you are discharged from the hospital, you are required to follow the doctor's advice for regular outpatient follow-up. At follow-up visits, the investigator will ask about your diet and measure your blood sugar. You will be contacted by telephone every 1 month to inquire about your postoperative recovery, diet, etc.

?

5. How the Study Ended

If you complete all study visits, the study will last for 24 months, and you will be scheduled for additional visits as needed during the study, after which you will be available at your usual frequency.

The study will conclude after the completion of the last subject's treatment, and it is anticipated that your time in the study may last 1-2 years.

You may opt out of the study at any time during the study, and the study physician may ask you to do so for your health and benefit. Prior to withdrawal, the study physician may order tests to ensure that you can exit safely. Your data will not be included in the results of the study, and your medical treatment and rights will not be affected.

 During the course of the study, study physicians, study funders, regulatory authorities, and ethics committees may terminate the study.

6. Study Benefits

Your surgical outcome and long-term quality of life may improve by participating in this study, but we cannot guarantee that you will. You will receive careful evaluation, monitoring, and treatment beyond routine monitoring.

Your participation in this study may help physicians learn more about the effects of treatment for high-risk insulinomas, information that other patients with the same or similar conditions may benefit from in the future.

7. Research Risks and inconveniences

There are known or unknown risks associated with any research. Some are mild and transient, some are severe and permanent, and whether and which risks arise and their severity will vary from person to person. Your research physician will take all precautions and monitor your condition closely. If you experience any discomfort, be sure to inform your study physician immediately so that necessary treatment can be taken promptly.

Risks of study-related procedures: Preoperative ERCP endoscopy and pancreatic duct stenting may pose risks of pancreatitis, perforation, bleeding, and stent migration. There are risks of pancreatic fistula, bleeding, and infection after surgery, and these risks are also risks in the process of disease treatment. Participation in this study does not increase the incidence of these risks.

Possible inconvenience of the study: To participate in this study, you need to strictly record the amount of drainage and the time of extubation. The rest were the same as routine. Patients were followed up 4 times on time after the operation and completed the examinations required by the experiment (the number and content of follow-up visits were the same as the recommended routine diagnosis and treatment process for postoperative patients). Please take these inconvenients into account when deciding whether to participate in this study.

8. Alternatives that can be adopted

If you do not participate in the study, you can choose to perform pancreaticoduodenectomy or enucleation with or without pancreatic stent placement, as is standard practice for insulinoma management at this hospital. Your study physician will explain to you the potential benefits and risks of treatment.

9. New information during the study

During the course of the study, the investigator has acquired important and up-to-date information relevant to the study. We will keep you informed and it is up to you to decide whether to continue participating in the study.

10. Study-related costs

If you are assigned to the experimental group, you may be responsible for some study-related costs, which primarily include the cost of endoscopic procedures (including pancreatic stent

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placement) that may be involved in the study. Regardless of whether you are assigned to the control group or the experimental group, medications and other routine tests are necessary in the course of routine clinical care and therefore will be paid for by you (or covered by medical insurance, if applicable). You will also have to pay for the treatment and tests you need for any coexisting medical conditions.

You will not be paid for your participation in the study, but the study will purchase clinical trial liability insurance for each patient who participates, which will be paid directly by the study investigators.

11. Study-related damages

If you experience any discomfort during the study, please contact the study doctor in time. The study doctor will guide you in the follow-up treatment. The researcher has purchased insurance for this study, and the insurance company will be responsible for the cost of treatment and reimbursement if you suffer any damage to your health as a result of participating in this study.

12. Confidentiality Policy

Your personal and medical information may be collected or processed in this study, including but not limited to: your name, gender, date of birth, address, telephone, diagnosis and treatment, examination, medical imaging, surgical records, etc.

Your personal information will be used only for the purposes described in the study protocol and this informed consent form.

Your medical information obtained by participating in this study will be kept confidential. The results of the study will also be published in academic journals without revealing any personally identifiable information about you.

?

13. Possible conflicts of interest from funding sources

This study was funded by the National High Level Hospital Clinical Research Funding of Peking Union Medical College Hospital, and there was no conflict of interest between the investigators and this study.

14. Voluntary Participation

Your participation is entirely voluntary. You may not participate or withdraw from the study at any time during the course of the study. This will not affect your relationship with the medical staff and your usual medical care will not be affected in any way.

15. Notes for Subjects

- Please tell the research doctor about your health status (especially whether you have other tumors and heart and lung diseases) and previous surgery history;
- Please follow the doctor's advice to the hospital on time for follow-up;
- If you feel any discomfort, please inform your research doctor in time;

16. Contact information

If you experience any discomfort, or if you have any questions about the study, you can contact the investigator at:

Position: Research physician	Name: Xu Qiang	Telephone number:
		13810096103

If you have any questions about your rights as a subject, you can contact the Ethics Committee at:

Position: Ethics Secretary	Name: Li Jiayue	Phone number: 010-
		69156874

Thank you for reading and considering participation in the study.

17. Signature page

Subject:

I confirm the following information:

(1) I have read and understood the informed information and have had sufficient time to consider participation in the study.

(2) All my questions have been satisfactorily answered.

(3) I voluntarily participated in the study and followed the study procedures.

(4) I understand that I can withdraw from the study at any time without giving a reason and that my treatment or rights will not be affected.

(5) I have received an informed consent form and signed consent form for my retention.

(6) I agree to have my sample collected and used as described in this informed consent.

(7) I give permission for my personal information to be collected and used in this study.

(8) I understand that I may be contacted in the future to obtain my permission for this study or any related substudy.

By signing this document, I agree to participate in the study as stated in the Informed Information and consent form.

Subject's name (in block letters) :

Signature of Subject: Date:

The following is limited to the subject who is incapacitated, and the signature of the guardian is required.

[Subject's name (in block letters), relationship between guardian and subject is.]

Guardian's name (in block letters) : Contact Number:

Signature of Guardian: Date:

The following is limited to subjects without the ability to read and write, and the signature of an impartial witness is required.

Witness's name (in block letters) : Contact Number:

Signature of Witness: Date:

Name of investigator/authorizer (in block letters) :

Signature of investigator/authorizer: Date:

8 / 8

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and

23
24 provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A,

Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and

Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

Reporting Item

artsson A, at mining, Al training, Al training, Page Number and 11.

Administrative

44	Administrativ
45	
46	information
47	
48	

Title

<u>#1</u>	Descriptive title identifying the study design,
	population, interventions, and, if applicable, trial

acronym

Trial registration <u>#2a</u> Trial identifier and registry name. If not yet registered,

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BMJ	Open

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		name of intended registry	
Trial registration:	<u>#2b</u>	All items from the World Health Organization Trial	
data set		Registration Data Set	
Protocol version	<u>#3</u>	Date and version identifier	
Funding	<u>#4</u>	Sources and types of financial, material, and other	
		support	
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors	
responsibilities:			
contributorship			
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor	
responsibilities:			
sponsor contact			
information			
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study	
responsibilities:		design; collection, management, analysis, and	
sponsor and funder		interpretation of data; writing of the report; and the	
		decision to submit the report for publication, including	
		whether they will have ultimate authority over any of	
		these activities	
Roles and	<u>#5d</u>	Composition, roles, and responsibilities of the	
responsibilities:		coordinating centre, steering committee, endpoint	
committees		adjudication committee, data management team, and	
		other individuals or groups overseeing the trial, if	
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		applicable (see Item 21a for data monitoring committee)
ntroduction		
Background and	<u>#6a</u>	Description of research question and justification for
ationale		undertaking the trial, including summary of relevant
		studies (published and unpublished) examining
		benefits and harms for each intervention
Background and	<u>#6b</u>	Explanation for choice of comparators
rationale: choice of		
comparators		
Objectives	<u>#7</u>	Specific objectives or hypotheses
Trial design	<u>#8</u>	Description of trial design including type of trial (eg,
		parallel group, crossover, factorial, single group),
		allocation ratio, and framework (eg, superiority,
		equivalence, non-inferiority, exploratory)
Methods:		
Participants,		
nterventions, and		
outcomes		
Study setting	<u>#9</u>	Description of study settings (eg, community clinic,
		academic hospital) and list of countries where data
		will be collected. Reference to where list of study sites
		can be obtained
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2-3

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1 2	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If		
3 4			applicable, eligibility criteria for study centres and		
5 6 7			individuals who will perform the interventions (eg,		
7 8 9			surgeons, psychotherapists)		
10 11 12	Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to		
13 14	description		allow replication, including how and when they will be		
15 16 17			administered		
18 19 20	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated		
21 22	modifications		interventions for a given trial participant (eg, drug		
23 24			dose change in response to harms, participant		
25 26 27			request, or improving / worsening disease)		
28 29	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention		
30 31 32	adherance		protocols, and any procedures for monitoring		
33 34 35			adherence (eg, drug tablet return; laboratory tests)		
36 37	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are		
38 39 40	concomitant care		permitted or prohibited during the trial		
41 42	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including		
43 44 45			the specific measurement variable (eg, systolic blood		
46 47			pressure), analysis metric (eg, change from baseline,		
48 49			final value, time to event), method of aggregation (eg,		
50 51			median, proportion), and time point for each outcome.		
52 53			Explanation of the clinical relevance of chosen		
54 55 56			efficacy and harm outcomes is strongly recommended		
57 58					
60		For peer re	er review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		
1 2	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including		
--	--	---------------------	---	--	--
3 4			any run-ins and washouts), assessments, and visits		
5 6 7			for participants. A schematic diagram is highly		
7 8 9 10			recommended (see Figure)		
11 12	Sample size	<u>#14</u>	Estimated number of participants needed to achieve		
13 14			study objectives and how it was determined, including		
15 16 17			clinical and statistical assumptions supporting any		
17 18 19 20			sample size calculations		
21 22	Recruitment	<u>#15</u>	Strategies for achieving adequate participant		
23 24 25			enrolment to reach target sample size		
26 27	Methods:				
28 29 30	Assignment of				
50					
31 32	interventions (for				
31 32 33 34 35	interventions (for controlled trials)				
31 32 33 34 35 36 37	interventions (for controlled trials) Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,		
31 32 33 34 35 36 37 38 39	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any		
 31 32 33 34 35 36 37 38 39 40 41 42 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 	interventions (for controlled trials) Allocation: sequence generation Allocation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 	interventions (for controlled trials) Allocation: sequence generation Allocation concealment	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,		
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 50 	interventions (for controlled trials) Allocation: sequence generation Allocation concealment mechanism	<u>#16a</u> #16b	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to		

		conceal the sequence until interventions are assigned
Allocation:	<u>#16c</u>	Who will generate the allocation sequence, who will
implementation		enrol participants, and who will assign participants to
		interventions
Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions
		(eg, trial participants, care providers, outcome
		assessors, data analysts), and how
Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is
emergency		permissible, and procedure for revealing a
unblinding		participant's allocated intervention during the trial
Methods: Data		
collection,		
management, and		
analysis		
Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome,
		baseline, and other trial data, including any related
		processes to promote data quality (eg, duplicate
		measurements, training of assessors) and a
		description of study instruments (eg, questionnaires,
		laboratory tests) along with their reliability and validity,
		if known. Reference to where data collection forms
		can be found, if not in the protocol
Data collection plan:	<u>#18b</u>	Plans to promote participant retention and complete
retention		follow-up, including list of any outcome data to be
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N/A

1			collected for participants who discontinue or deviate
2 3 4			from intervention protocols
5 6 7	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,
8 9			including any related processes to promote data
10 11			quality (eg, double data entry; range checks for data
12 13			values). Reference to where details of data
14 15 16			management procedures can be found, if not in the
17 18			protocol
19 20 21	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and
22 23			secondary outcomes. Reference to where other
24 25 26			details of the statistical analysis plan can be found, if
20 27 28			not in the protocol
29 30 31	Statistics: additional	<u>#20b</u>	Methods for any additional analyses (eg, subgroup
32 33 34	analyses		and adjusted analyses)
35 36	Statistics: analysis	<u>#20c</u>	Definition of analysis population relating to protocol
37 38 39	population and		non-adherence (eg, as randomised analysis), and any
40 41	missing data		statistical methods to handle missing data (eg,
42 43			multiple imputation)
44 45 46 47	Methods: Monitoring		
48 49	Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);
50 51 52	formal committee		summary of its role and reporting structure; statement
52 53 54			of whether it is independent from the sponsor and
55 56			competing interests; and reference to where further
57 58			details about its charter can be found, if not in the
59 60	F	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

	protocol. Alternatively, an explanation of why a DMC	ВМЈ Ор
	is not needed	en: fir
<u>#21b</u>	Description of any interim analyses and stopping	N/A publ
	guidelines, including who will have access to these	ished
	interim results and make the final decision to	as 10.1 Prote
	terminate the trial	ected by
<u>#22</u>	Plans for collecting, assessing, reporting, and	iopen-2 N/Ayrig
	managing solicited and spontaneously reported	023-07 yht, inc
	adverse events and other unintended effects of trial	8516 c ;ludinç
	interventions or trial conduct	on 2 Apr Er y for use
<u>#23</u>	Frequency and procedures for auditing trial conduct, if	il 2024. ss relate N/A
	any, and whether the process will be independent	Downl ment \$ 9d to te
	from investigators and the sponsor	oaded Superie sxt and
		from <mark>h</mark> sur (AB I data m
		ttp://bi ES) . nining,
	0.	njope Al trai
<u>#24</u>	Plans for seeking research ethics committee /	n.bmj. 1 ^{ning} ,
	institutional review board (REC / IRB) approval	com/ o and si
<u>#25</u>	Plans for communicating important protocol	milar te N/Aar te
	modifications (eg, changes to eligibility criteria,) 13, 20 9chnol
	outcomes, analyses) to relevant parties (eg,)25 at , ogies.
	investigators, REC / IRBs, trial participants, trial	Agenc
	registries, journals, regulators)	e Biblic
<u>#26a</u>	Who will obtain informed consent or assent from	ographique З
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Data monitoring:

interim analysis

Harms

Auditing

Ethics and

approval

Protocol

amendments

Consent or assent

dissemination

Research ethics

1			potential trial participants or authorised surrogates,
2 3			and how (see Item 32)
4 5 6	Consent or assent:	#26b	Additional consent provisions for collection and use of
7 8		<u></u>	
9 10	anciliary studies		participant data and biological specimens in ancillary
10 11 12			studies, if applicable
12 13 14	Confidentiality	<u>#27</u>	How personal information about potential and enrolled
15 16			participants will be collected, shared, and maintained
17 18			in order to protect confidentiality before, during, and
19 20			after the trial
21 22			
23 24	Declaration of	<u>#28</u>	Financial and other competing interests for principal
25 26	interests		investigators for the overall trial and each study site
27 28			
29 30	Data access	<u>#29</u>	Statement of who will have access to the final trial
31 32			dataset, and disclosure of contractual agreements
33 34			that limit such access for investigators
35 36			2
37 38	Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and
39 40	trial care		for compensation to those who suffer harm from trial
40 41			participation
42 43			
44 45	Dissemination	<u>#31a</u>	Plans for investigators and sponsor to communicate
46 47	policy: trial results		trial results to participants, healthcare professionals,
48 49			the public, and other relevant groups (eg, via
50 51			publication, reporting in results databases, or other
52 53 54			data sharing arrangements), including any publication
55 56			restrictions
57 58			
59 60		For peer re	eview only - http://bmjopen.bmi.com/site/about/quidelines.xhtml
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1 2	Dissemination	<u>#31b</u>	Authorship eligibility guidelines and any intended use	880 7 0
3	policy: authorship		of professional writers	pen: fir:
5 6 7	Dissemination	<u>#31c</u>	Plans, if any, for granting public access to the full	st publis 7 liis
8 9 10	policy: reproducible		protocol, participant-level dataset, and statistical code	shed as
11 12	research			10.1136 rotecte
13 14 15 16	Appendices			id by copy
17 18	Informed consent	<u>#32</u>	Model consent form and other related documentation	See supplement
19 20 21	materials		given to participants and authorised surrogates	ntal materials
22 23	Biological	<u>#33</u>	Plans for collection, laboratory evaluation, and	g for us N/Au
24 25 26	specimens		storage of biological specimens for genetic or	ril 202 es rela
27 28			molecular analysis in the current trial and for future	1. Dow ated to
29 30 21			use in ancillary studies, if applicable	nloade : Super text ar
32 33	The SPIRIT Explanat	tion and	Elaboration paper is distributed under the terms of the Cre	ative ative ative
34 35 36	Commons Attribution	License	CC-BY-NC. This checklist was completed on 14. May 202	23 using
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Study Protocol for Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct: a multicenter randomized Clinical Trial in Chinese Tertiary Medical Centers

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-078516.R3
Article Type:	Protocol
Date Submitted by the Author:	19-Feb-2024
Complete List of Authors:	Gao, Ruichen; Peking Union Medical College Hospital, General surgery; Peking Union Medical College, 8-year MD program Yin, Bohui; Peking Union Medical College Hospital; Peking Union Medical College, 8-year MD program Jin, Jiabin; Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital Tian, Xiaodong; Peking University First Hospital, Department of General Surgery Zhang, Yuhua; Zhejiang Provincial People's Hospital, Division of Hepatobiliary and Pancreatic Surgery and Minimally Invasive Surgery Wei, Jishu; The First Affiliated Hospital With Nanjing Medical University, Pancreas Center Cao, Feng; Xuanwu Hospital Wang, Zheng; The First Affiliated Hospital of Xi'an Jiaotong University, Department of Hepatobiliary Surgery Ma, Zhijun; Panjin People's Hospital Wang, Min; Huazhong University of Science and Technology Tongji Medical College Tongji Hospital, Department of Biliary-Pancreatic Surgery, Gou, Shanmiao; Huazhong University of Science and Technology Tongji Medical College First Clinical College Union Hospital, Department of Pancreatic Surgery Cong, Lin; Peking Union Medical College Hospital, General surgery Xu, Qiang; Peking Union Medical College Hospital, General Surgery Wu, Wenming; PUMCH, Department of General Surgery Zhao, Yupei; Peking Union Medical College Hospital
Primary Subject Heading :	Surgery
Secondary Subject Heading:	Surgery, Diabetes and endocrinology
Keywords:	Pancreatic surgery < SURGERY, Pancreatic disease < GASTROENTEROLOGY, Endocrine tumours < ONCOLOGY

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Zhao Yupei, zhao8028@263.net * These authors contributed equally # Corresponding Author Abstract Introduction The surgical intervention approach to insulinomas in proximity to the main pancreatic duct remains controversial. Standard pancreatic resection is recommended by several guidelines; however, enucleation (EN) still attracts surgeons with less risk of late exocrine/endocrine insufficiency, despite a higher postoperative pancreatic fistula (POPF) rate. Recently, the efficacy and safety of preoperative pancreatic stents placement before the enucleation have been demonstrated. Thus, a multicenter open-label study is being conducted to evaluate the efficacy and safety of stents placement in improving the outcome of enucleation of insulinomas in proximity to the main pancreatic duct.

Methods and analysis

This is a prospective, randomized, open-label, superiority clinical trial conducted at multiple tertiary centers in China. The major eligibility criteria is the presence of insulinoma located in the head and neck of the pancreas in proximity(≤2mm) to the main pancreatic duct. Blocked randomization will be performed to allocate patients into the Stent EN group and the Direct EN group. Patients in the Stent EN group will go through stent placement by the endoscopist within 24 hours before the enucleation surgery, whereas other patients will receive enucleation surgery directly. The primary outcome is the assessment of the superiority of stent placement in reducing POPF rate

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measured by the International Study Group of Pancreatic Surgery (ISGPS) standard.
Both interventions will be performed in an inpatient setting and regular follow-up will
be performed. The primary outcome (POPF rate) will be tested for superiority with the
Chi-square test. The difference in secondary outcomes between the two groups will be
analyzed using appropriate tests.

Ethics and dissemination

The study ha been approved by the Peking Union Medical College Hospital Institutional Review Board (K23C0195), Ruijin Hospital Ethics Committee (2023-314), Peking University First Hospital Ethics Committee (2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical University (2023223-002), Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473). Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929), and Shanghai Cancer Center Institutional Review Board (2309282-16). The results of the study will be published in an international peer-reviewed journal.

- 80 <u>Trial registration number</u>
- 81 ClinicalTrials. gov Registry (NCT05523778).

Keywords: Insulinoma, pancreatic duct stent, enucleation, postoperative pancreatic

83 fistula

84 Article Summary

- 85 Strengths and limitations of this study
 - 86 > A prospective multicenter clinical design to assess the efficacy and safety of a

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3 4	07	proventive intervention in improving the outcome of equalection surgery
5	07	preventive intervention in improving the outcome of endcleation surgery.
6		
7	88	Recruiting patients from multiple tertiary medical centers across China.
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9	89	> Local online communication tool exploited to promote interactions between
10 11		
12	90	investigators and patients
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14	01	The leak of blinding of the nationte surgeone, data collectors, and data analysts
15	91	
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17	92	is the limitation of the study.
18 10		
20	93	Introduction
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22	94	Insulinomas are the most common functioning pancreatic neuroendocrine neoplasms, with
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24	05	an actimated incidence of 1.4 per million per year [1, 2] They are inculin correting tumore
25 26	95	an estimated incidence of 1-4 per minior per year [1, 2] They are insum-secreting tumors
20		
28	96	that cause common clinical features including neuroglycopenia and autonomic nervous
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30	97	system disorders caused by dysregulated secretion of insulin[3-5]. Surgical management
31		
32 33	98	remains the only curative modality for 90% of benign, localized insulinomas[4, 6].
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35	aa	According to several guidelines including the National Comprehensive Cancer Network
36	00	According to several guidelines moldaling the National comprehensive calleer Network
37	400	(NOON) and the Evene and Neuropean destine Turner Original (ENIETS) (7, 0) and the time (ENI)
38	100	(NCCN) and the European Neuroendocrine Tumor Society (ENETS)[7, 8], enucleation(EN),
39 40		
40	101	a parenchymal preserving modality, that could reduce the risk of late exocrine/endocrine
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43	102	insufficiency, should be considered as the first-line surgical approach for exophytic and
44		
45	103	peripheral insulinomas[9]
46	100	
47	101	l la companya di su da su da su di su d
49	104	However, in cases of endopristic insulinomas or tumors in proximity to the main pancreatic
50		
51	105	duct (MPD), the optimal choice of surgical intervention is controversial. Standard
52		
53 54	106	pancreatic resection, such as pancreaticoduodenectomy (PD) and distal pancreatectomy
55		
56	107	(DP), is indicated in guidelines while they aggressively eliminate normal pancreatic tissue.
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58	108	which can lead to long-term consequences including experine and endocrine panerostic
59	100	which can lead to long-term consequences including exocilite and endocrine particleatic
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109	insufficiency [10, 11]. Recently, duodenum-preserving pancreatic head resection (DPPHR)
110	was alternatively recommended for the resection of large PNETS.[12] In contrast,
111	performing EN in cases with endophytic insulinomas and tumors in proximity to the MPD
112	still baffles many surgeons as several retrospective researches suggested a significantly
113	elevated rate of postoperative morbidity, especially postoperative pancreatic fistula(POPF).
114	Lu et.al compared postoperative morbidity between PD and EN, indicating a significant
115	difference in POPF (18.1% vs 61.1%) between the two approaches[13], and Heeger K et
116	al. reported the POPF rate as 70% (21 of 30 patients) after EN of pancreatic tumors
117	located ≤3 mm from the MPD [14]. Another study involving 52 patients who underwent EN
118	also demonstrated a high POPF rate of 60% in the group of tumors located at less than or
119	equal to 2 mm from the MPD.[15]. Recently, Dokmak et.al suggested the proximity to MPD
120	< 3 mm as an independent risk factor of POPF in enucleation[16]. Therefore, preventive
121	measures in EN that decrease the POPF rate would encourage the implementation of EN
122	thus improving the long-term benefits for patients with insulinomas in proximity to the MPD.
123	POPF is usually derived from intraoperative injuries to MPD. Prophylactic preoperative
124	stenting is believed to prevent the MPD injury in that it not only helps to identify the location
125	of MPD in the surgical field thus preventing intraoperative damage but also decompresses
126	pancreatic duct by reducing pancreatic juice leakage from the resection plane and
127	providing support to the duct when stricture develops. Pertinent clinical evidence involving
128	stenting and EN is still lacking. Some researchers reported the usage of preoperative
129	stenting as a prophylaxis for EN[17-21], and despite they all revealed the feasibility and
130	safety of the technique, most of these researches involved a limited number of patients

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4	131	and were single-armed studies.
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0	132	Based on the knowledge and shortcomings on this topic, our team has collected 18
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9	100	
10	133	patients undergoing preoperative stenting in our center for 5 years. We retrospectively
10		
12	134	analyzed the risk factor of postoperative complications, especially POPF, and discovered
13		
14	405	that the distance from including to MDD <0 mm uses on independent side for the for DODE
15	135	that the distance from insulinoma to MPD ≤ 2 mm was an independent risk factor for POPF
16		
17	136	(OR =6.011, p = 0.003). In addition, the preoperative pancreatic stent substantially reduced
18		
19	407	the incidence of DODE is noticety with tweever leasted in previously to the MDD (27.5% we
20	137	the incidence of POPF in patients with tumors located in proximity to the MPD (37.5% vs
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22	138	71.4%, p = 0.028) [22]. Therefore, we launched the current clinical trial to assess the
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25	139	efficacy and safety of preoperative stenting before EN of insulinoma in the head and heck
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27	140	of the pancreas in proximity to the MPD. According to the Evidence Map of Pancreatic
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3U 21	141	Surgery (<u>www.evidencemap.surgery</u>), this is the first trial of its kind[23].
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32 33	142	Methods and analysis
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153	> Endpoints
154	Primary endpoint: Rate of POPF within 3 months after EN.
155	Secondary endpoints:
156	1) Rate of post-stent-placement acute pancreatitis in Stented EN group within in 3 weeks
157	after EN
158	2) Operation time
159	3) Intraoperative blood loss
160	4) Rate of postoperative abdominal infection within 3 weeks after EN
161	5) Rate of postpancreatectomy hemorrhage(PPH) within 3 weeks after EN
162	6) Rate of postoperative lung infection within 3 weeks after EN
163	7) Rate of postoperative delayed gastric emptying within 3 weeks after EN
164	8) Rate of postoperative dyspepsia within 6 months after EN
165	9) Rate of postoperative hyperglycemia within 6 months after EN
166	10) Total cost of hospitalization
167	> Definition
168	In this study, POPF, delayed gastric emptying and PPH adopt the definition proposed by
169	the International Pancreatic Surgery Research Group (ISGPS) [24-26]. Pancreatitis,
170	abdominal infection, dyspepsia, lung infection, and hyperglycemia will be evaluated
171	based on Common Terminology Criteria for Adverse Event (CTCAE) V.5.0. Severe
172	adverse events are defined as grade 3 or higher in CTCAE.
173	Patients eligibility

174 Inclusion and exclusion criteria are shown in Box 1

176 Randomization will be initiated by authorized investigators of the trial after checking the 177 informed consent and the inclusion and exclusion criteria. Each eligible patient will be 178 allocated an individual code/randomization number, which has to be recorded in case 179 report form (CRF). Blocked randomization (blocked number=4) for each center will be 180 performed using SAS Studio by the study assistant prior to the beginning of enrollment. 181 After randomization, surgeons in all centers who enroll the patient will be informed of the 182 intervention assignment.

C C

183 > Blindness

Following recent academic recommendations on the implementation of blinding in surgical trials[27], meticulous consideration has been given to blinding strategies tailored to distinct study contributors, which encompass patients, surgeons, data collectors, data analysts, and outcome assessors. Patients participating in this study are deemed unblindable due to the intrinsic procedural difference between the two groups. Surgeons, who possess a direct line of sight to the presence of the stent during intraoperative procedures, are similarly unfeasible candidates for blinding. Data collectors also find themselves in a position where blinding is not viable, primarily due to the inevitable nature of their responsibilities, which involve the encounter of specific clinical data and records that are integral to prompt group allocation results. Examples of such records are operation records of stenting procedures and diagnostic CT imaging, which may conclusively reveal the presence of a stent within MPD. Furthermore, the integrity of data analysis relies on the unobstructed knowledge of group allocation results, rendering the blinding of data analysts

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> 197 unviable. Recognizing the critical importance of blinding in assessing primary and 198 secondary endpoints, especially those related to complications, outcome assessors are 199 kept blinded to participant group allocation. Based on our protocol, the assessment of 200 endpoints is directly linked with objective clinical data which can be provided to 201 independent assessors with blindness of allocation. This strategy plays a pivotal role in 202 reducing potential bias in the assessment of primary and secondary outcomes while 203 concurrently insulating the operating surgeon from subjective judgment regarding clinical 204 endpoints. Emergency unblinding is not deemed necessary.

205 ➤ Study interventions

206 After baseline visit and admission, eligible participants will be randomized to the stented 207 EN group or the direct EN group, as shown in Figure 1.

Preoperative MPD stenting

209 The preoperative pancreatic duct stent was regarded as a possible effective method to 210 prevent POPF. The single-pigtail pancreatic duct stent is usually placed within 24 hours 211 before the enucleation endoscopically. The stent length should span the site of the tumor. 212 The length and the diameter of the stent used will be recorded in CRF. The stent will 213 beremoved by duodenoscopy about three months after surgery. Endoscopic stent 214 placement and removal represent a common procedure at the Endoscopic Center of 215 Peking Union Medical College Hospital and other centers and will be carried out by 216 experienced endoscopists (minimum of 50 procedures) for the study. Any adverse events 217 will be recorded in CRF including stent-related pancreatitis. Blood amylase will be tested

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218 2-4 hours after stenting before enucleation to discover potential stenting-related acute219 pancreatitis.

Enucleation

During the surgery, intraoperative ultrasound will be performed to evaluate the location of the tumor and the distance between the tumor and MPD. The peripheral pancreatic lobule covering the tumor will be exposed by the ultrasound scalpel. After exposure of the insulinoma, the surgeon will suture the lesion and suspend it, and then the insulinoma will be dissected from the normal pancreatic tissue. Dissection will be performed in contact with the lesion by a combination of harmonic scalpel and bipolar cautery. Frozen sections of resected specimens will be regularly investigated to identify benign insulinomas. The operative field will be carefully examined and MPD disruption will be repaired immediately once detected. The prophylactic abdominal drainage tube will be applied. Intraoperative conversion (to open procedure, DPPHR, or PD), surgery time, blood loss, and transfusion volume will be recorded in CRF.

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Postoperative management

General clinical treatment and PF prevention treatment will be conducted in both two groups. The patient's body temperature and drainage volume were recorded daily. The amount and the amylase concentration of the drainage fluid as well as the blood will be routinely measured on the 1st, 3rd, 5th, and 7th postoperative days. Extubation would be considered if the drainage volume is less than 10 ml for 3 consecutive days or the amylase level of the drainage solution is less than three times the upper limit of normal. If the

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drainage tube has not been removed at the time of discharge, the patient will be instructedto record the daily drainage until extubation in the outpatient setting.

Follow-up

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242 For the first three months after discharge, patients should maintain a regular follow-up 243 session every two weeks through outpatient or telephone. The following information will be 244 collected during each follow-up: basic information and the general condition of the patient, 245 whether the patient has been extubated (if not extubated, record the recent drainage condition), recent medical interventions, and possible manifestations of dyspepsia or 246 247 hyperglycemia. Laboratory tests and imaging examinations will be done at the surgeon's 248 discretion. Normally, CT or MRI scans will be performed routinely at 3 months 249 postoperatively, just before stent removal, and then again 3 months after the stent removal.

250 > Statistical methods

Hypothesis

Null hypothesis

253 The rate of POPF in patients who undergo MPD stent placement before enucleation 254 is not less than that of patients who undergo enucleation directly.

102

Alternative hypothesis

256 The rate of POPF in patients who undergo MPD stent placement before enucleation

- is less than that of patients who undergo enucleation directly.
 - 258 Sample size calculation

5 259 In our previous retrospective study, a total of 44 patients with insulinoma in proximity to the

260 MPD who underwent enucleation were included, of which 16 had stent placement and 28

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had no stent placement, and the number of patients with POPF was 6 (37.5%) and 20 (71.4%), respectively. According to the abovementioned POPF rate in two conditions, 38 evaluable patients per group will provide 85% power to reject the null hypothesis in a Z test (unpooled) for superiority at a one-sided significance level of 0.05 considering the POPF rate difference of at least 5% to represent a clinically relevant difference. Therefore, 78 patients in total are to be recruited in the study considering possible dropout.

Statistical analysis

The primary outcome (rate of POPF) will be tested for superiority with a Chi-square test assuming a superiority difference of 5% with a one-sided significance level of 0.05. All patients undergoing EN will be included. The analysis will be performed twice: firstly after about 50% of the patients have been discharged and secondly after all patients have finished the follow-up procedure. Secondary outcomes will be described by calculating means or relative frequencies for each treatment group with 95% Cls. Differences in secondary outcomes between two groups will be analyzed using appropriate tests (Shapiro-Wilk tests, t-tests, Mann-Whitney U tests, Wilcoxon rank-sum tests, Chi-square tests, Fisher's exact tests, etc.).

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277 Ethics and dissemination

Written informed consent from all the patients screened will be obtained before the
procedures start. The study protocol has been approved by the Peking Union Medical
College Hospital Institutional Review Board (approval number K23C0195), Ruijin Hospital
Ethics Committee (2023-314), Peking University First Hospital Ethics Committee
(2024033-001), Institutional Review Board of Xuanwu Hospital of Capital Medical

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> University (2023223-002), Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2023LSK-473), Institutional Review Board of Tongji Medical College Tongji Hospital (TJ-IRB202402059), Ethics Committee of Tongji Medical College Union Hospital (2023-0929), and Shanghai Cancer Center Institutional Review Board (2309282-16) and registered in ClinicalTrials.gov(NCT05523778). The study will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki [28]. Throughout the study, all data acquired in this trial will be provided to the involved investigators and ethics committee members for monitoring, audits, and inspections. Results will be published in an international peer-reviewed journal. In response to the submission and approval of our protocol, several modifications have been incorporated into the study design, all of which have undergone thorough scrutiny and received approval from our ethics committee. Firstly, a new timepoint at postoperative day 7 (pod7) has been added for the measurement of amylase levels, leveraging the existing practice of routinely measuring amylase levels for all patients at this time point. Secondly, we have introduced an exclusion criterion based on the maximum diameter of the tumor (>2cm), a feasible addition given that no enrolled patients before this change met the exclusion criteria. Thirdly, a significant refinement involves blinding outcome assessors, a practicable adjustment as assessors can re-evaluate outcomes solely based on the information recorded in the case report form (CRF). Lastly, we have clarified that the primary outcome measurement will occur at 90 days postoperatively, enhancing precision in reporting the study's findings. These modifications aim to strengthen the study's scientific integrity, participant safety, and overall methodological rigor.

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305 > Patient and public involvement

Throughout the study, a study account based on a local online communication tool (WeChat) will be established to receive any suggestions and consultations from patients involved and information about the study will be updated for all patients who subscribed to the study account.

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Discussion

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312 Generally, enucleation is preferred over other operation approaches in treating insulinomas, 313 as it circumvents complicated reconstructions and possible subsequent complications. 314 However, POPF is common in the enucleation of insulinomas that are in proximal to MPD, 315 which limits its clinical application. In this clinical trial, we aim to demonstrate the safety 316 and efficacy of preoperative stenting as a prophylaxis for EN. Several observational studies 317 have shown promising effects of MPD stent in the prevention of POPF but with limited 318 evidence. In this study, we aim to include patients who are prone to suffer from POPF to 319 validate the efficacy of MPD stent. In our previous research, we demonstrated the distance 320 from insulinoma to MPD ≤2 mm was an independent risk factor for POPF. Therefore, it is 321 a reasonable and feasible choice to confine patients whose tumors are "deep" in our 322 ongoing trial. Preoperative MPD stent placement, as an extra intervention procedure for 323 treating insulinoma, is still a vague yet practical technique in the prevention of POPF. Thus, 324 the conduction of this clinical trial in a randomized controlled way is under the general 325 ethical principle of clinical equipoise according to our present knowledge. In this way, the 326 result of this multicenter, prospective, randomized control clinical trial can offer substantial

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327	information on the feasibility of this approach,	and thus hopefully widen the indication of

- 328 enucleation and partially alter the treatment pathway of insulinoma.
- 329

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330 Author Contributions

- 331 <u>Contributors</u> GR, YB, CL, XQ, WW, ZY participated in creating the study design. GR
 332 drafted the manuscript. JJ, TX, ZY, WJ, CF, WZ, MZ, WM, GS provided a critical revision
- of the manuscript. XQ obtained the funding for this study. All the authors read and approved
- 334 the final manuscript.
- 335 *Funding* The trial will be supported by a grant from the National High Level Hospital Clinical
- 336 Research Funding(2022-PUMCH-A-050).
 - 337 <u>Disclaimer</u> The funder will have no role in the conduct or analysis of the trial.
 - 338 <u>Competing interests</u> None declared.
- 339

340 Total word count: 2654

341 Figure 1 Flow chart of the study. FBG, fasting blood glucose; HbA1c, glycosylated

- 342 hemoglobin; INS, insulin; C-pep, C-peptide; CE-CT, contrast-enhanced CT; US,
 - 343 ultrasound; DM, diabetes mellitus; ASA American Society of Anesthesiology.
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55 56					s is clear, and	it was determ	med that the tumor is	single,
57 58			The distance bet	woon the	tumor and th	e main noncro	atic duct is determine	d to be
59			≤ 2 mm by preop	erative in	naging (enhan	ced CT. MRI	etc.):	
60					- 3		/)]

2			
3	\succ Truly informed and voluntarily participate in this study, with written informed		
4	encent		
6	consent.		
7	Exclusion Criteria		
8	Maximum diameter of the tumor >2cm proved pathologically		
9	Severe cardionulmonary complications		
10 11			
12	Combined with other known tumor diseases		
13	Invasive insulinoma or insulinoma with suspicious metastasis		
14	Previous upper abdominal surgery history		
15	Refusal or inability to cooperate in the study		
10			
18 4	33		
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20 4	34		
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23 <u>4</u>	35		
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Written	informed consent form
Medical Research	Preoperative Pancreatic Stents
Topics:	Placement Before the Enucleation of
	Insulinoma Located in the Head and
	Neck of the Pancreas in Proximity to
	the Main Pancreatic Duct
Protocol number	
(if applicable):	
Study Site:	Peking Union Medical College Hospital,
	Chinese Academy of Medical Sciences
Principal	Qiang Xu
investigators:	
Informed consent	V3.0
form Version No.	
Informed consent	2022/12/30

1 2		
3 4 5 6	form version date	
7 8 9 10	Subject Name:	
11 12 13 14	Subject ID:	
16 17 18		
20 21 22 23		
24 25 26 27		
28 29 30 31		
32 33 34 35		
36 37 38 39		
40 41 42 43		
44 45 46 47		
48 49 50 51		
52 53 54 55		
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60		

Dear Subject:

We would like to invite you to participate in a clinical study entitled "A Randomized Controlled Study of Preoperative Pancreatic Stents Placement Before the Enucleation of Insulinoma Located in the Head and Neck of the Pancreas in Proximity to the Main Pancreatic Duct ".

Before you decide whether to consent to participate, please read this informed consent form carefully and ask the investigators questions about your concerns. You may also ask your family, friends, or others. Once you have decided to participate in the study, you will be asked to sign this informed consent form.

1. Research Background

Insulinoma is the most common type of functional pancreatic endocrine tumors, which is characterized by uncontrolled excessive insulin secretion. Its main treatment is surgical resection. 90% of patients with insulinoma can be cured by surgical treatment. We found that for insulinomas located in the pancreatic head and neck near the main pancreatic duct, enucleation is prone to cause main pancreatic duct injury, which increases the risk of postoperative pancreatic fistula and other serious complications. Therefore, pancreaticoduodenectomy is recommended, but it requires combined resection of part of the stomach, duodenum, common bile duct and gallbladder, and there is a high risk of postoperative pancreatic exocrine insufficiency. In contrast, enucleation still has the advantages of less trauma and low incidence of long-term postoperative pancreatic secretion insufficiency, which is of great help to improve the long-term quality of life of patients after surgery. At present, the surgical management of this type of tumor is still inconclusive in the world, and many large pancreatic centers are still conducting clinical studies on enucleation. Studies have shown that preoperative placement of pancreatic duct stents followed by enucleation can reduce the incidence of postoperative pancreatic fistula and increase the long-term postoperative benefits, but the placement of pancreatic duct stents may cause stent-related adverse events. However, the placement of pancreatic stent may cause stent-related adverse events. However, there is no high-level clinical study to demonstrate its advantages and disadvantages. Therefore, the aim of this study is to investigate the safety and efficacy of preoperative pancreatic stent placement in patients with insulinoma in the pancreatic head and neck near the main pancreatic duct through a multi-center randomized controlled trial, so as to provide evidence-based medical evidence for standardized treatment of insulinoma and thus to change the current treatment guidelines.

This study was approved by the Peking Union Medical College Hospital Ethics Committee.

2. What was the purpose of this clinical study?

To compare the clinical efficacy, safety and efficacy between direct enucleation and preoperative placement of pancreatic stent followed by enucleation for insulinoma near the main pancreatic duct in the head and neck of the pancreas, and to evaluate the application value of the former surgical treatment strategy.

3. Methods: Study

This study was an intervention study. Participants were divided into two groups: experimental

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group and control group. Enrollment in the two groups is 1:1, grouping will be random (like a lottery), and neither you nor the investigator can choose in advance which group to participate in. The study was unblinded, meaning that after randomization, you, the investigator, and the clinician knew which group you had been assigned to. The study had an anticipated enrollment of 78 patients nationwide.

4. Study PROCESS

 Before commencing any research related activities, you will first need to sign this informed consent form.

During the screening period, the researcher will ask and collect your personal information, previous diagnosis and treatment, your combined medications, comorbidities, and order your blood routine, liver function, renal function, pancreatic function, fasting blood glucose, insulin, C-peptide, abdominal and pelvic enhanced CT, MRI and other examinations. We will determine whether you meet the inclusion criteria through your current clinical symptoms, performance, and examination results.

If you meet the eligibility criteria, study treatment will be initiated, and you will be randomly assigned to either an experimental group (placement of a pancreatic duct stent before enucleation) or a control group (enucleation alone). You will then proceed to endoscopic stent placement and surgery according to standard protocols.

During your hospitalization, we will collect your laboratory test results, surgery-related information, and recovery, which do not require your additional cooperation. If you are assigned to the experimental group, you will be scheduled to undergo ERCP-guided pancreatic duct stenting approximately 1 day before the procedure, which is in accordance with the usual practice of our hospital.

After you are discharged from the hospital, you are required to follow the doctor's advice for regular outpatient follow-up. At follow-up visits, the investigator will ask about your diet and measure your blood sugar. You will be contacted by telephone every 1 month to inquire about your postoperative recovery, diet, etc.

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5. How the Study Ended

If you complete all study visits, the study will last for 24 months, and you will be scheduled for additional visits as needed during the study, after which you will be available at your usual frequency.

The study will conclude after the completion of the last subject's treatment, and it is anticipated that your time in the study may last 1-2 years.

You may opt out of the study at any time during the study, and the study physician may ask you to do so for your health and benefit. Prior to withdrawal, the study physician may order tests to ensure that you can exit safely. Your data will not be included in the results of the study, and your medical treatment and rights will not be affected.

 During the course of the study, study physicians, study funders, regulatory authorities, and ethics committees may terminate the study.

6. Study Benefits

Your surgical outcome and long-term quality of life may improve by participating in this study, but we cannot guarantee that you will. You will receive careful evaluation, monitoring, and treatment beyond routine monitoring.

Your participation in this study may help physicians learn more about the effects of treatment for high-risk insulinomas, information that other patients with the same or similar conditions may benefit from in the future.

7. Research Risks and inconveniences

There are known or unknown risks associated with any research. Some are mild and transient, some are severe and permanent, and whether and which risks arise and their severity will vary from person to person. Your research physician will take all precautions and monitor your condition closely. If you experience any discomfort, be sure to inform your study physician immediately so that necessary treatment can be taken promptly.

Risks of study-related procedures: Preoperative ERCP endoscopy and pancreatic duct stenting may pose risks of pancreatitis, perforation, bleeding, and stent migration. There are risks of pancreatic fistula, bleeding, and infection after surgery, and these risks are also risks in the process of disease treatment. Participation in this study does not increase the incidence of these risks.

Possible inconvenience of the study: To participate in this study, you need to strictly record the amount of drainage and the time of extubation. The rest were the same as routine. Patients were followed up 4 times on time after the operation and completed the examinations required by the experiment (the number and content of follow-up visits were the same as the recommended routine diagnosis and treatment process for postoperative patients). Please take these inconvenients into account when deciding whether to participate in this study.

8. Alternatives that can be adopted

If you do not participate in the study, you can choose to perform pancreaticoduodenectomy or enucleation with or without pancreatic stent placement, as is standard practice for insulinoma management at this hospital. Your study physician will explain to you the potential benefits and risks of treatment.

9. New information during the study

During the course of the study, the investigator has acquired important and up-to-date information relevant to the study. We will keep you informed and it is up to you to decide whether to continue participating in the study.

10. Study-related costs

If you are assigned to the experimental group, you may be responsible for some study-related costs, which primarily include the cost of endoscopic procedures (including pancreatic stent

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placement) that may be involved in the study. Regardless of whether you are assigned to the control group or the experimental group, medications and other routine tests are necessary in the course of routine clinical care and therefore will be paid for by you (or covered by medical insurance, if applicable). You will also have to pay for the treatment and tests you need for any coexisting medical conditions.

You will not be paid for your participation in the study, but the study will purchase clinical trial liability insurance for each patient who participates, which will be paid directly by the study investigators.

11. Study-related damages

If you experience any discomfort during the study, please contact the study doctor in time. The study doctor will guide you in the follow-up treatment. The researcher has purchased insurance for this study, and the insurance company will be responsible for the cost of treatment and reimbursement if you suffer any damage to your health as a result of participating in this study.

12. Confidentiality Policy

Your personal and medical information may be collected or processed in this study, including but not limited to: your name, gender, date of birth, address, telephone, diagnosis and treatment, examination, medical imaging, surgical records, etc.

Your personal information will be used only for the purposes described in the study protocol and this informed consent form.

Your medical information obtained by participating in this study will be kept confidential. The results of the study will also be published in academic journals without revealing any personally identifiable information about you.

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13. Possible conflicts of interest from funding sources

This study was funded by the National High Level Hospital Clinical Research Funding of Peking Union Medical College Hospital, and there was no conflict of interest between the investigators and this study.

14. Voluntary Participation

Your participation is entirely voluntary. You may not participate or withdraw from the study at any time during the course of the study. This will not affect your relationship with the medical staff and your usual medical care will not be affected in any way.

15. Notes for Subjects

- Please tell the research doctor about your health status (especially whether you have other tumors and heart and lung diseases) and previous surgery history;
- Please follow the doctor's advice to the hospital on time for follow-up;
- If you feel any discomfort, please inform your research doctor in time;

16. Contact information

If you experience any discomfort, or if you have any questions about the study, you can contact the investigator at:

Position: Research physician	Name: Xu Qiang	Telephone number:
		13810096103

If you have any questions about your rights as a subject, you can contact the Ethics Committee at:

Position: Ethics Secretary	Name: Li Jiayue	Phone number: 010-
		69156874

Thank you for reading and considering participation in the study.
17. Signature page

Subject:

I confirm the following information:

(1) I have read and understood the informed information and have had sufficient time to consider participation in the study.

(2) All my questions have been satisfactorily answered.

(3) I voluntarily participated in the study and followed the study procedures.

(4) I understand that I can withdraw from the study at any time without giving a reason and that my treatment or rights will not be affected.

(5) I have received an informed consent form and signed consent form for my retention.

(6) I agree to have my sample collected and used as described in this informed consent.

(7) I give permission for my personal information to be collected and used in this study.

(8) I understand that I may be contacted in the future to obtain my permission for this study or any related substudy.

By signing this document, I agree to participate in the study as stated in the Informed Information and consent form.

Subject's name (in block letters) :

Signature of Subject: Date:

The following is limited to the subject who is incapacitated, and the signature of the guardian is required.

[Subject's name (in block letters), relationship between guardian and subject is.]

Guardian's name (in block letters) : Contact Number:

Signature of Guardian: Date:

The following is limited to subjects without the ability to read and write, and the signature of an impartial witness is required.

Witness's name (in block letters) : Contact Number:

Signature of Witness: Date:

Name of investigator/authorizer (in block letters) :

Signature of investigator/authorizer: Date:

8 / 8

 Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and

provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A,

Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D, SPIRIT 2013 Explanation and

Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

Reporting Item

acronym

#1

#2a

Administrative

information

Trial registration

Title

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Descriptive title identifying the study design,

population, interventions, and, if applicable, trial

Trial identifier and registry name. If not yet registered,

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		name of intended registry
Trial registration:	<u>#2b</u>	All items from the World Health Organization Trial
data set		Registration Data Set
Protocol version	<u>#3</u>	Date and version identifier
Funding	<u>#4</u>	Sources and types of financial, material, and other
		support
Roles and	<u>#5a</u>	Names, affiliations, and roles of protocol contributors
responsibilities:		
contributorship		
Roles and	<u>#5b</u>	Name and contact information for the trial sponsor
responsibilities:		
sponsor contact		
information		
Roles and	<u>#5c</u>	Role of study sponsor and funders, if any, in study
responsibilities:		design; collection, management, analysis, and
sponsor and funder		interpretation of data; writing of the report; and the
		decision to submit the report for publication, including
		whether they will have ultimate authority over any of
		these activities
Roles and	<u>#5d</u>	these activities Composition, roles, and responsibilities of the
Roles and responsibilities:	<u>#5d</u>	these activities Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint
Roles and responsibilities: committees	<u>#5d</u>	these activities Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and
Roles and responsibilities: committees	<u>#5d</u>	these activities Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if

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		applicable (see Item 21a for data monitoring committee)
Introduction		
Background and	<u>#6a</u>	Description of research question and justification for
rationale		undertaking the trial, including summary of relevant
		studies (published and unpublished) examining
		benefits and harms for each intervention
Background and	<u>#6b</u>	Explanation for choice of comparators
rationale: choice of		
comparators		
Objectives	<u>#7</u>	Specific objectives or hypotheses
Trial design	<u>#8</u>	Description of trial design including type of trial (eg,
		parallel group, crossover, factorial, single group),
		allocation ratio, and framework (eg, superiority,
		equivalence, non-inferiority, exploratory)
Methods:		
Participants,		
interventions, and		
outcomes		
Study setting	<u>#9</u>	Description of study settings (eg, community clinic,
		academic hospital) and list of countries where data
		will be collected. Reference to where list of study sites
		can be obtained
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1 2	Eligibility criteria	<u>#10</u>	Inclusion and exclusion criteria for participants. If
3 4			applicable, eligibility criteria for study centres and
5 6 7			individuals who will perform the interventions (eg,
, 8 9			surgeons, psychotherapists)
10 11 12	Interventions:	<u>#11a</u>	Interventions for each group with sufficient detail to
13 14	description		allow replication, including how and when they will be
15 16 17			administered
18 19 20	Interventions:	<u>#11b</u>	Criteria for discontinuing or modifying allocated
20 21 22	modifications		interventions for a given trial participant (eg, drug
23 24			dose change in response to harms, participant
25 26 27			request, or improving / worsening disease)
28 29	Interventions:	<u>#11c</u>	Strategies to improve adherence to intervention
30 31 32	adherance		protocols, and any procedures for monitoring
33 34 35			adherence (eg, drug tablet return; laboratory tests)
36 37	Interventions:	<u>#11d</u>	Relevant concomitant care and interventions that are
38 39 40	concomitant care		permitted or prohibited during the trial
41 42	Outcomes	<u>#12</u>	Primary, secondary, and other outcomes, including
43 44 45			the specific measurement variable (eg, systolic blood
46 47			pressure), analysis metric (eg, change from baseline,
48 49			final value, time to event), method of aggregation (eg,
50 51 52			median, proportion), and time point for each outcome.
52 53 54			Explanation of the clinical relevance of chosen
55 56			efficacy and harm outcomes is strongly recommended
57 58 59			
60	I	or peer re	eview only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2	Participant timeline	<u>#13</u>	Time schedule of enrolment, interventions (including
3 4			any run-ins and washouts), assessments, and visits
5 6 7			for participants. A schematic diagram is highly
7 8 9 10			recommended (see Figure)
11 12	Sample size	<u>#14</u>	Estimated number of participants needed to achieve
13 14			study objectives and how it was determined, including
15 16 17			clinical and statistical assumptions supporting any
17 18 19 20			sample size calculations
21 22	Recruitment	<u>#15</u>	Strategies for achieving adequate participant
23 24 25			enrolment to reach target sample size
26 27	Methods:		
28 29 30	Assignment of		
50			
31 32	interventions (for		
31 32 33 34 35	interventions (for controlled trials)		
31 32 33 34 35 36 37	interventions (for controlled trials) Allocation: sequence	<u>#16a</u>	Method of generating the allocation sequence (eg,
31 32 33 34 35 36 37 38 39	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any
 31 32 33 34 35 36 37 38 39 40 41 42 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 	interventions (for controlled trials) Allocation: sequence generation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 	interventions (for controlled trials) Allocation: sequence generation Allocation	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 	interventions (for controlled trials) Allocation: sequence generation Allocation concealment	<u>#16a</u>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,
 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 50 	interventions (for controlled trials) Allocation: sequence generation Allocation concealment mechanism	<u>#16a</u> #16b	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to

10

			conceal the sequence until interventions are assigned
3	Allocation:	<u>#16c</u>	Who will generate the allocation sequence, who will
5	implementation		enrol participants, and who will assign participants to
, 3 9			interventions
0 1 2	Blinding (masking)	<u>#17a</u>	Who will be blinded after assignment to interventions
3 4			(eg, trial participants, care providers, outcome
5 6 7			assessors, data analysts), and how
8 9	Blinding (masking):	<u>#17b</u>	If blinded, circumstances under which unblinding is
.0 21 22	emergency		permissible, and procedure for revealing a
23 24 25	unblinding		participant's allocated intervention during the trial
26 27	Methods: Data		
28 29 30	collection,		
81 82	management, and		
33 34 35	analysis		
6 7	Data collection plan	<u>#18a</u>	Plans for assessment and collection of outcome,
88 89			baseline, and other trial data, including any related
1 1			processes to promote data quality (eg, duplicate
13 14			measurements, training of assessors) and a
15 16			description of study instruments (eg, questionnaires,
17 18			laboratory tests) along with their reliability and validity,
19 50			if known. Reference to where data collection forms
51 52 53			can be found, if not in the protocol
54 55	Data collection plan:	<u>#18b</u>	Plans to promote participant retention and complete
b6			
56 57 58	retention		follow-up, including list of any outcome data to be
6 7 8 9	retention	or peer re	follow-up, including list of any outcome data to be eview only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

N/A

1			collected for participants who discontinue or deviate
2 3 4			from intervention protocols
5 6	Data management	<u>#19</u>	Plans for data entry, coding, security, and storage,
7 8 9			including any related processes to promote data
10 11			quality (eg, double data entry; range checks for data
12 13			values). Reference to where details of data
14 15			management procedures can be found, if not in the
16 17 18			protocol
19 20 21	Statistics: outcomes	<u>#20a</u>	Statistical methods for analysing primary and
21 22 23			secondary outcomes. Reference to where other
24 25			details of the statistical analysis plan can be found, if
26 27 28			not in the protocol
20 29 30	Statistics: additional	#205	Mathada far any additional analyses (og. subgroup
31 32		#200	and adjusted analyses (eg, subgroup
33 34	analyses		and adjusted analyses)
35 36 27	Statistics: analysis	<u>#20c</u>	Definition of analysis population relating to protocol
37 38 39	population and		non-adherence (eg, as randomised analysis), and any
40 41	missing data		statistical methods to handle missing data (eg,
42 43			multiple imputation)
44 45 46 47	Methods: Monitoring		
48 49	Data monitoring:	<u>#21a</u>	Composition of data monitoring committee (DMC);
50 51 52	formal committee		summary of its role and reporting structure; statement
52 53 54			of whether it is independent from the sponsor and
55 56			competing interests; and reference to where further
57 58			details about its charter can be found, if not in the
59 60	F	or peer re	view only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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protocol. Alternatively, an explanation of why a DN is not needed Data monitoring: **#21b** Description of any interim analyses and stopping interim analysis guidelines, including who will have access to these interim results and make the final decision to terminate the trial #22 Plans for collecting, assessing, reporting, and Harms managing solicited and spontaneously reported adverse events and other unintended effects of tria interventions or trial conduct Auditing #23 Frequency and procedures for auditing trial conduction any, and whether the process will be independent from investigators and the sponsor Ethics and dissemination Research ethics #24 Plans for seeking research ethics committee / approval institutional review board (REC / IRB) approval Protocol #25 Plans for communicating important protocol amendments modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) #26a Who will obtain informed consent or assent from Consent or assent

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		potential trial participants or authorised surrogates,
		and how (see Item 32)
Consent or assent:	<u>#26b</u>	Additional consent provisions for collection and use of
ancillary studies		participant data and biological specimens in ancillary
		studies, if applicable
Confidentiality	<u>#27</u>	How personal information about potential and enrolled
		participants will be collected, shared, and maintained
		in order to protect confidentiality before, during, and
		after the trial
Declaration of	<u>#28</u>	Financial and other competing interests for principal
interests		investigators for the overall trial and each study site
Data access	<u>#29</u>	Statement of who will have access to the final trial
		dataset, and disclosure of contractual agreements
		that limit such access for investigators
Ancillary and post	<u>#30</u>	Provisions, if any, for ancillary and post-trial care, and
trial care		for compensation to those who suffer harm from trial
		participation
Dissemination	<u>#31a</u>	Plans for investigators and sponsor to communicate
policy: trial results		trial results to participants, healthcare professionals,
		the public, and other relevant groups (eg, via
		publication, reporting in results databases, or other
		data sharing arrangements), including any publication
		restrictions
	For peer re	eview only - http://bmiopen.bmi.com/site/about/quidelines.xhtml

Discomination	#24b	Authorship clicibility guidelines and enviotended use	7
Dissemination	<u>#310</u>	Authorship eligibility guidelines and any intended use	/
policy: authorship		of professional writers	
Dissemination	<u>#31c</u>	Plans, if any, for granting public access to the full	7
policy: reproducible		protocol, participant-level dataset, and statistical code	-
research			
Appendices			
Informed consent	<u>#32</u>	Model consent form and other related documentation	See suppleme
materials		given to participants and authorised surrogates	ntal materials
Biological	<u>#33</u>	Plans for collection, laboratory evaluation, and	N/A
specimens		storage of biological specimens for genetic or	
		molecular analysis in the current trial and for future	
		use in ancillary studies, if applicable	
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https://www.goodrepo	orts.org/	, a tool made by the <u>EQUATOR Network</u> in collaboration	with
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