Trials

STUDY PROTOCOL

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WONDER-02: plastic stent vs. lumen-apposing metal stent for endoscopic ultrasound-guided drainage of pancreatic pseudocysts—study protocol for a multicentre randomised non-inferiority trial

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Abstract

Background Endoscopic ultrasound (EUS)-guided transluminal drainage has become a first-line treatment modality for symptomatic pancreatic pseudocysts. Despite the increasing popularity of lumen-apposing metal stents (LAMSs), plastic stents may resolve non-necrotic fluid collections effectively with lower costs and no LAMS-specific adverse events. To date, there has been a paucity of data on the appropriate stent type in this setting. This trial aims to assess the non-inferiority of plastic stents to a LAMS for the initial EUS-guided drainage of pseudocysts.

Methods The WONDER-02 trial is a multicentre, open-label, non-inferiority, randomised controlled trial, which will enrol pancreatic pseudocyst patients requiring EUS-guided treatment in 26 centres in Japan. This trial plans to enrol 80 patients who will be randomised at a 1:1 ratio to receive either plastic stents or a LAMS (40 patients per arm). In the plastic stent group, EUS-guided drainage will be performed using two 7-Fr double pigtail stents. In the LAMS group, the treatment will be performed in the same way except for LAMS use. The step-up treatment will be performed via endoscopic and/or percutaneous procedures at the trial investigator's discretion. The primary endpoint is clinical success, which is defined as a decrease in a pseudocyst size to ≤ 2 cm and an improvement in inflammatory

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indicators (i.e. body temperature, white blood cell count, and serum C-reactive protein). Secondary endpoints include technical success, adverse events including mortality, pseudocyst recurrence, and medical costs.

Discussion The WONDER-02 trial will investigate the efficacy and safety of plastic stents compared to a LAMS in EUS-guided treatment of symptomatic pancreatic pseudocysts with a particular focus on the non-inferior efficacy of plastic stents. The findings will help establish a new treatment algorithm for this population.

Trial registration ClinicalTrials.gov NCT06133023 registered on 9 November 2023. UMIN000052647 registered on 30 October 2023. jRCT1032230444 registered on 7 November 2023.

Keywords Drainage, Endoscopy, Endosonography, Mortality, Pancreatic fistula, Pancreatic pseudocyst, Pancreatitis, Randomised clinical trial, Sepsis, Stents

Introduction

Background and rationale {6a}

Pancreatic fluid collections (PFCs) develop as local complications of acute pancreatitis after 4 weeks of the disease onset [1–3]. Pancreatic pseudocysts are a type of PFC, which is characterised by encapsulated fluid with minimal or no necrotic contents. Pseudocysts occasionally become symptomatic (e.g. infection, gastrointestinal symptoms), and given the high morbidity and mortality, it is mandatory to manage symptomatic pseudocysts appropriately to improve clinical outcomes of patients with acute pancreatitis overall [1, 4, 5]. Endoscopic ultrasound (EUS)-guided transluminal drainage has become a first-choice treatment option for symptomatic PFCs [6–10]. In the setting of EUS-guided treatment of walled-off necrosis (WON, the other type of PFC), the potential benefits of lumen-apposing metal stents (LAMSs) have been reported [11, 12]. Compared to plastic stents, LAMSs can serve as a transluminal port and thereby, facilitate the treatment of WON that often requires a long treatment duration with repeated interventions including direct endoscopic necrosectomy [13, 14]. Several retrospective studies have reported the feasibility of LAMS use for EUS-guided drainage of pseudocysts [15, 16]. In line with the growing popularity and availability of LAMSs in interventional EUS overall, LAMSs are increasingly used to treat pseudocysts without robust supporting evidence for their effectiveness compared to plastic stents.

While a LAMS may enhance the drainage efficiency of pseudocysts due to its large calibre, the benefits of this stent may be mitigated in pseudocysts that, by definition, contain minimal or no necrotic liquid contents and can be managed without necrosectomy [6, 17]. In other words, plastic stents may resolve pseudocysts effectively without any additional interventions. Indeed, several retrospective comparative studies failed to demonstrate the superiority of a LAMS to plastic stents [6, 16, 18–20]. In a study of 205 patients with pancreatic pseudocysts, the stent types were not correlated with the rate of clinical success in the multivariable analysis [16]. In another investigation of 21 patients, there was no significant difference in the rates of treatment success and adverse events between the LAMS and plastic stent groups [18]. In addition, the use of a LAMS has been limited by higher costs compared to plastic stents [18, 20] and potential specific adverse events (e.g. bleeding, buried stent) [21–23]. A randomised trial suggests that a prolonged duration of LAMS placement (approximately ≥ 3 weeks [24]) may predispose the patients to an elevated risk of adverse events associated with LAMSs. Therefore, patients requiring long-term drainage (e.g. cases with disconnected pancreatic duct syndrome [25, 26]) should be subjected to a reintervention in which a LAMS is replaced by a plastic stent. However, the technical success rate of the replacement has not been high [27]. Given these lines of evidence, we hypothesised that plastic stents might be non-inferior to a LAMS in terms of the potential of resolving a pseudocyst and associated symptoms.

To test our hypothesis, we have planned a multicentre randomised controlled trial (RCT) to examine the non-inferiority of plastic stents to a LAMS as the initial stent for EUS-guided drainage of pancreatic pseudocysts in terms of the achievement of clinical treatment success (the resolution of a pseudocyst). Given the lower costs of plastic stents compared to a LAMS, the results would help not only establish a new treatment paradigm for pancreatic pseudocysts but also improve the cost-effectiveness of the resource-intensive treatment.

Objectives {7}

The primary objective of the WONDER-02 trial is to evaluate the non-inferiority of plastic stents to a LAMS placed during the initial EUS-guided drainage of a pancreatic pseudocyst in terms of the rate of clinical success. The main secondary objectives include the assessments of a technical success rate, time to clinical success, and procedure-related adverse events including mortality, costs, and long-term outcomes (detailed in Table 1).

Table 1 The primary and secondary endpoints in the WONDER-02 trial

	Definition
Primary endpoint	
Clinical success (within 180 days of randomisation)	A decrease in the size of a targeted pancreatic pseudocyst to 2 cm or less with an improvement of at least two out of the following inflammatory indicators for patients receiving EUS-guided drainage for infected pseudocysts: body temperature (< 37.0 °C), white blood cell count (normalisation or > 50% decrease), and C-reactive protein (normalisation or > 50% decrease). A decrease in the size of a targeted pancreatic pseudocyst to 2 cm or less with relief of symptoms associated with a pseudocyst for patients receiving EUS-guided drainage for non-infectious symptomatic pseudocysts. Requirement of salvage surgical interventions will be considered as clinical failure
Secondary endpoints	
Technical success of the initial EUS-guided drainage	Successful placement of any stent in the targeted pseudocyst during the initial EUS-guided drainage
Time to clinical success	Time from randomisation to the achievement of clinical success
Procedure-related AEs[a]	Defined and graded as mild, moderate, or severe, according to the ASGE lexicon guidelines for AEs of endoscopic procedures [28]
Length of hospitalisation	Time from randomisation to discharge
Mortality from any cause	In-hospital mortality
Exploratory endpoints	
Procedure-related outcomes	
Number of interventions	Total number of endoscopic, percutaneous, angiographic and surgical procedures until the achievement of clinical success
Total procedure time	Total procedure time until the achievement of clinical success
Duration of antibiotics administration	Time from randomisation to the cessation of antibiotics (for patients receiving EUS-guided drainage for infected pseudocysts)
Requirement of surgical interventions	Salvage surgical interventions (e.g. debridement, drainage, cystogastrostomy) required to achieve clinical success
Total costs of interventions and hospitalisation	Total costs related to treatment including costs of procedures, accessary devices, stents, and inpatient care. The costs will be considered during a period from randomisation to discharge. Procedure-related costs will be estimated based on the procedure reimbursement and the costs of accessary devices and stents
Long-term outcomes (assessed at 5 years of randomisation and end of follow-up)	
Incidence of pseudocyst recurrence	Occurrence of a new pseudocyst or exacerbation of the treated pseudocyst on cross-sectional imaging studies following clinical success
Time to pseudocyst recurrence	Time from clinical success to a recurrence of a pseudocyst
Incidence of new-onset diabetes	Incidence of new-onset diabetes (haemoglobin A1c ≥ 6.5%, or the initiation of an antidiabetic agent) during follow-up
Incidence of clinical symptoms associated with pancreatic exocrine insufficiency	Incidence of new-onset clinical symptoms associated with pancreatic exocrine insufficiency during follow-up. Clinical symptoms are steatorrhea, malnutrition, indigestion, and weight loss that are assumed to be a result from pancreatic exocrine insufficiency
Incidence of pancreatic cancer	Incidence of new-onset pancreatic cancer during follow-up
Incidence of sarcopenia	Incidence of sarcopenia defined as low levels of skeletal muscle index evaluated based on a CT image at the level of the third vertebra (< 42 cm^2/m^2 for men and < 38 cm^2/m^2 for women) [29]
Changes in the morphology and volume of the pancreas	Changes in the morphology and volume of the pancreas evaluated via CT images [30]

Abbreviations: *AE* adverse event, *ASGE* American Society for Gastrointestinal Endoscopy, *CT* computed tomography, *EUS* endoscopic ultrasound

Bleeding: Haematemesis and/or melena or haemoglobin drop > 2 g/dL. Perforation: Evidence of air or luminal contents outside the gastrointestinal tract. Because of the nature of the procedure, asymptomatic pneumoperitonitis is not included. Pancreatitis: Typical pain with amylase/lipase > 3 times normal. Others: Other procedure-related events requiring conservative and interventional treatment

[a] Adverse events include bleeding, perforation, pancreatitis, and others

Trial design {8}

The WONDER-02 trial has been designed as a multicentre, open-label, parallel-group, randomised controlled trial that aims to evaluate the non-inferiority of plastic stents to a LAMS in terms of clinical success among patients receiving EUS-guided drainage of pancreatic pseudocysts. Patients diagnosed with symptomatic pseudocysts will be screened for the inclusion and exclusion criteria. Eligible patients will be randomised at a 1:1 ratio to either the plastic stent group or the LAMS group.

The WONDER-02 trial has been designed and will be implemented by the WONDERFUL (WON anD pERi-pancreatic FlUid coLlection) study group in Japan, which consisted of expert endoscopists, gastroenterologists, interventional radiologists, and epidemiologists at high-volume centres in Japan [5, 6, 8, 25, 31–33].

Methods: participants, interventions, and outcomes

Study setting {9}

The WONDER-02 trial will be conducted at tertiary care centres in Japan. Therefore, data will be collected and analysed in Japan. The participating sites recruiting trial participants are listed in Appendix.

Eligibility criteria {10}

The inclusion and exclusion criteria for patient eligibility are presented in Table 2. Eligible patients must meet all inclusion criteria and none of the exclusion criteria to be enrolled.

Study endoscopists at the participating centres (the study investigators) will perform interventions for both groups.

Who will take informed consent? {26a}

The trial investigators (treating endoscopists who have been registered in a trial protocol approved by the corresponding centre) will obtain written informed consent from potential trial participants or authorised surrogates using the latest version of the approved consent form.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

N/a. We will obtain additional approval from the institutional review board (IRB) in case we use the study data for secondary purposes in future studies. Participants will be provided with a chance for informed consent or opt-out, as appropriate. The protocol of the WONDER-02 trial does not require the research use of biospecimens from the participants.

Interventions

Explanation for the choice of comparators {6b}

In the WONDER-02 trial, the experimental intervention is the EUS-guided transluminal placement of plastic stents for a pancreatic pseudocyst, and the control

Table 2 Eligibility criteria for participants with pancreatic pseudocysts in the WONDER-02 trial (eligible patients must meet all inclusion criteria and none of the exclusion criteria to be enrolled)

Inclusion criteria
Patients with pancreatic pseudocyst(s) defined by the revised Atlanta classification[a]
The longest diameter of a targeted pseudocyst ≥ 5 cm
Patients requiring drainage for symptoms associated with a pseudocyst (e.g. infection[b], gastrointestinal symptoms including abdominal pain, or jaundice)
Patients aged 18 years or older
Written informed consent obtained from patients or their representatives
Exclusion criteria
A pseudocyst that is inaccessible via the EUS-guided approach
A plastic or lumen-apposing metal stent in situ
Coagulopathy (e.g. platelet count < 50,000/mm^3 or PT-INR > 1.5)
Users of antithrombotic agents that cannot be discontinued according to the JGES guidelines
Patients with active gastrointestinal bleeding
Patients with symptomatic or subclinical ileus
Patients who do not tolerate endoscopic procedures
Pregnant women

Abbreviations: *EUS*, endoscopic ultrasound; *JGES*, Japan Gastroenterological Endoscopy Society; *PFC*, pancreatic fluid collection; *PT-INR*, prothrombin time international normalised ratio

[a] Patients with non-necrotic PFCs (e.g. postoperative PFCs) may be included

[b] The presence of infection will be determined clinically based on symptoms (e.g. fever and abdominal pain), elevated levels of inflammatory markers (e.g. white blood cell count and C-reactive protein), and/or blood culture. Infection will be considered present in patients with a positive culture of aspirated cyst fluid

intervention is the placement of a LAMS. With the growing popularity of LAMSs in EUS-guided drainage of pancreatobiliary diseases including PFCs [17, 34, 35], this modality is currently used as a treatment option for large-size pancreatic pseudocysts at many centres. Compared to plastic stents, LAMSs may provide better drainage efficiency due to their large calibre. However, no prospective studies have shown the superiority of LAMSs over plastic stents in terms of the rate of clinical treatment success with mixed results from retrospective investigations [16, 18]. On the other hand, a LAMS should be replaced with a plastic stent in cases where long-term drainage is required (e.g. cases with disconnected pancreatic duct syndrome [25–27, 36]). In addition, LAMS placement may result in specific adverse events and is limited by high costs. Compared to WON, pseudocysts contain non-necrotic fluid contents, which may be drained sufficiently via a plastic stent without the need for a LAMS.

Intervention description {11a}

In both experimental and control groups, EUS-guided drainage of pancreatic pseudocysts will be performed on an inpatient basis. EUS-guided drainage will be conducted under endosonographic and fluoroscopic guidance within 72 h of the randomisation. A linear echoendoscope will be advanced to the stomach or duodenum with conscious sedation, and the targeted pseudocyst will be visualised and punctured under endosonographic guidance. Plastic stents or LAMS will be placed according to the allocated group. Prophylactic antibiotics may be administered at the trial investigator's discretion.

In cases with an insufficient improvement in inflammatory indicators (i.e. body temperature, white blood cell count, and C-reactive protein), we will perform additional interventions including the addition of or replacement with a plastic stent or LAMS [37] and/or percutaneous drainage [38] if needed.

Experimental intervention: EUS-guided drainage of a pseudocyst using plastic stents

In the plastic stent group, two (at least one) 7-Fr double pigtail stents will be placed. Following the EUS-guided puncture of a pseudocyst, a guidewire will be coiled within the lesion, and another guidewire will be inserted alongside the prepositioned guidewire. The puncture tract will be dilated if needed.

Control intervention: EUS-guided drainage of a pseudocyst using a LAMS

In the LAMS group, a LAMS with electrocautery enhanced delivery will be placed (Hot AXIOS; Boston Scientific Japan, Tokyo, Japan). The diameter of a LAMS will be determined at the endoscopist's discretion (10 mm, 15 mm, and 20 mm are commercially available at the time of writing). A guidewire or dilator will be used if needed.

Criteria for discontinuing or modifying allocated interventions {11b}

Allocated interventions will be discontinued or modified after the randomisation in cases that:

1. Participants withdraw their consent.
2. Participants are considered ineligible (not satisfying the eligibility criteria).
3. Participants cannot continue to receive the allocated intervention due to worsened symptoms of pseudocysts (e.g. sepsis), worsened comorbidities, or severe adverse events.
4. Participants become pregnant.
5. The WONDER-02 trial is terminated.
6. The discontinuation or modification of the allocated intervention is considered necessary from the clinical perspective.

Strategies to improve adherence to interventions {11c}

In the plastic stent group, it may be technically difficult to place two plastic stents through the puncture tract during the initial EUS-guided drainage. In difficult cases, we will use a balloon or bougie dilator to dilate the tract.

Relevant concomitant care permitted or prohibited during the trial {11d}

All relevant concomitant care and interventions can be administered according to the local clinical practice during the trial interventions. In general, antibiotics are administered until clinical success for infected pseudocysts cases, and prophylactic antibiotics are administered in the periprocedural period for non-infected cases. In cases without adverse events, oral intake will be resumed on the next day of EUS-guided drainage.

Provisions for post-trial care {30}

In cases with clinical success, plastic stents or a LAMS will be removed at approximately 4 weeks of stent placement when a puncture tract is expected to be matured. Given the potential adverse events (AEs) associated with prolonged LAMS placement [24, 39], a LAMS will be removed or replaced with plastic stent(s) at approximately 4 weeks of stent placement. In cases with confirmed (or suspected) disconnected pancreatic duct syndrome, long-term placement of a plastic stent may be considered.

Outcomes {12}

Table 1 summarises the primary and secondary outcome measures in the WONDER-02 trial. The primary endpoint is clinical success in the treatment of a targeted pancreatic pseudocyst. Clinical success is defined as (1) a decrease in a pseudocyst size to 2 cm or less (based on serial images of computed tomography [CT]) with (2) an improvement of at least two out of the three inflammatory indicators (i.e. body temperature [< 37.0 °C], white blood cell count [normalisation or > 50% decrease], and C-reactive protein [normalisation or > 50% decrease]) for patients receiving EUS-guided drainage for infected pseudocysts. Also, clinical success is defined as (1) a decrease in a pseudocyst size to 2 cm or less (based on serial images of CT with (2) relief of symptoms associated with a pseudocyst for patients receiving EUS-guided drainage for non-infectious symptomatic pseudocysts. Clinical success will be considered achieved whether additional non-surgical interventions are required or not. Patients who require salvage surgical interventions for pseudocysts or undergo clinical success after 180 days of the randomisation will be treated as cases with clinical failure (no clinical success). We will evaluate clinical success as the primary endpoint because this outcome measure is correlated with the duration of a treatment period and thus a burden on patients and the health care system. The percentage of clinical success will be used to evaluate the overall treatment efficacy of a given intervention.

Participant timeline {13}

A schematic diagram of the time course for participants of the WONDER-02 trial is illustrated in Fig. 1.

Sample size {14}

For the sample size calculation, we assumed that the rates of clinical success of EUS-guided drainage were 93.5% in the plastic stent group and 95% in the LAMS group according to preliminary data from our retrospective analysis within the WONDERFUL study group (under submission). Seventy-four patients were assumed to be required with the following parameters: randomisation rate, 1:1; non-inferiority margin, 15%; one-sided α level, 0.05; and power, 0.80. Taking the dropout into account (a dropout rate of approximately 8%), we planned a sample size of 80 participants (40 participants per arm).

Recruitment {15}

Trial investigators at each institution will create a list of consecutive patients presenting with pancreatic pseudocysts regardless of the requirement of interventional

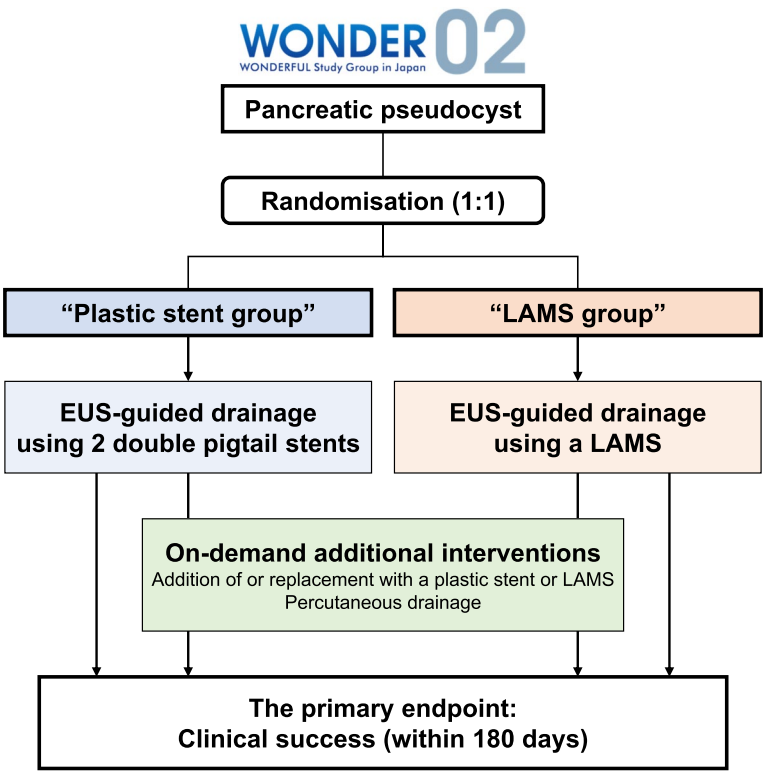

Fig. 1 Flow diagram summarising the experimental and control interventions that are examined in the WONDER-02 trial. Abbreviations: EUS, endoscopic ultrasound; LAMS, lumen-apposing metal stent

treatment and screen all the patients for the eligibility criteria of the WONDER-02 trial. The principal investigator will create a webpage to introduce the current trial to neighbouring hospitals and increase referrals and transfers. For cases with equivocal CT findings in terms of eligibility, the expert panel consisting of seven gastroenterologists and two board radiologists will hold an online meeting or e-mail communication upon consultation and make a decision within 24 h.

Assignment of interventions: allocation

Sequence generation {16a}

Eligible patients with pancreatic pseudocysts will be allocated randomly to either the plastic stent group (experimental group) or the LAMS group (control group) based on a random sequence generated by the web-based system (University Hospital Medical Information Network Internet Data and Information System for Clinical and Epidemiological Research, cloud version [UMIN INDICE Cloud], https://www.umin.ac.jp/indice/cloud.html). The UMIN clinical trial registration system has been approved as an acceptable registry by the International Committee of Medical Journal Editors. The WONDER-02 trial employs the minimisation method with the institutions and aetiology of pancreatic pseudocysts (acute pancreatitis vs. no [including postoperative PFCs and unknown causes]) as allocation factors. Given potential variations in patient characteristics and clinical practice between the participating centres [5], the randomisation will be done with the institutions as an allocation factor.

Concealment mechanism {16b}

The web-based randomisation system will be utilised, and therefore, the randomisation process will be concealed completely.

Implementation {16c}

Trial investigators at the corresponding centres will enrol eligible patients and register them to the web-based randomisation system, which will allocate the participants to trial interventions.

Assignment of interventions: blinding

Who will be blinded {17a}

Due to the nature of the experimental and control interventions, the participants and investigators will not be blinded to the allocated groups. Only statisticians will be blinded.

Procedure for unblinding if needed {17b}

N/a. The participants and investigators will not be blinded to the assigned groups.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The outcome variables (the primary and secondary endpoints) and the variables associated with clinical characteristics have been pre-defined. To increase the quality of data on the primary endpoint (i.e. clinical success), the expert panel will review the clinical course and CT images upon request. Data on those variables will be collected from the electronic medical chart at each centre. The schedule of enrolment, randomisation, interventions, and assessments is summarised in Table 3.

The trial investigators at each centre will collect data on patients' baseline characteristics and treatment outcomes from the electronic medical chart and input anonymised data to the trial database. The standardised trial database has been constructed using the Microsoft Access software (Microsoft Corp., Tokyo, Japan) and has been distributed to participating centres. The database file will be uploaded to the online storage that can be accessed only by the investigators. The data manager will download and combine the data files. The information on the allocations to the experimental and control arms will be collected from the computerised randomisation system. Using the fake ID numbers specific to this trial, the primary investigator will link the datasets.

Plans to promote participant retention and complete follow-up {18b}

The enrolled patients will undergo all interventions on an inpatient basis and will be requested to visit the outpatient clinic at least once a month after discharge. There are no available reminder systems for outpatient visits (e.g. text messages). However, when patients do not make a scheduled visit, the investigators will call the patients to follow up on the patient's conditions and make a subsequent appointment.

Data management {19}

The trial investigators will upload anonymised patient data to the online storage. The data manager will download and combine the files and then store the integrated database in a password-locked stand-alone computer at the research management office in the Clinical Research Centre at The University of Tokyo Hospital (Tokyo, Japan). In the management office, the collected data will be stored in a server with the RAID (Redundant Array of Independent Disks) 1 configuration (also known as mirroring for a back-up). The data manager will also screen for missing or unplausible data and ask the corresponding investigator at each centre for a data check.

Table 3 Schedule of the study interventions and clinical assessments in the WONDER-02 trial

	Study period					
	Pre-intervention	Intervention (within 180 days of randomisation)				Post-intervention
	≤ 10 days before randomisation		Within 3 days of randomisation	Every 7 days after the intervention[a]	After 180 days of the intervention	After 5 years of clinical success
	Screening	Randomisation	Intervention	Assessment	Assessment	Follow-up
Informed consent	X					
Eligibility screening	X					
Assessment of pseudocysts	X					
Assessment of symptoms	X				X	
Body temperature	X			X	X	
Blood test[b]	X			X	X	
Imaging study[c]	X			X[d]	X	
Electrocardiogram	X					
Randomisation		X				
Interventions (EUS-guided drainage)			X			
Assessment of the primary endpoint					X	
Assessment of secondary endpoints				X	X	X
Monitoring of adverse events				X	X	X

[a] After discharge, we will follow patients up at least once a month at the clinic with a computed tomography with a 3-month interval

[b] A blood test will include the following items: white blood cell count, haemoglobin, platelet count, albumin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, amylase, lipase, blood urea nitrogen, creatinine, C-reactive protein, and the international normalised ratio of prothrombin time

[c] Contrast-enhanced computed tomography will be performed unless there are contraindications for contrast use. Magnetic resonance imaging may be performed at the trial investigator's discretion

[d] Imaging studies will be evaluated every 2–3 weeks during the intervention period

Abbreviation: *EUS*, endoscopic ultrasound

The document of data management procedures has been approved by the IRB at The University of Tokyo Hospital.

Confidentiality {27}

All patient data will be anonymised with a fake ID number that will be assigned to each potential or enrolled participant as soon as they are collected. The corresponding investigator at each centre will store the list matching the fake and hospital ID numbers in a password-locked stand-alone computer. All communications between the investigators at each centre, the principal investigator, and the data manager will be done using fake ID numbers.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/a. In the WONDER-02 trial, biospecimens will not be collected for research on genetic or molecular characteristics.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

In the primary analysis, we will compare the proportions of clinical success between the plastic stent and LAMS groups in the intention-to-treat population. The non-inferiority of plastic stents to a LAMS will be considered statistically significant when the lower limit of 90% confidence interval for a difference in the proportions of clinical success between the plastic stent and LAMS groups is above the non-inferiority margin (i.e. − 15%). Confidence intervals of the rates of clinical success will be calculated based on the exact method [40]. In secondary analyses, cumulative probabilities of times to clinical success will be estimated using the Kaplan–Meier product-limit method and be compared using the log-rank test. Patients are censored at the last follow-up, 180 days of the randomisation, or death, whichever comes first. A Cox proportional hazards regression model will be used to calculate hazard ratios for clinical success. In analyses of other outcomes, continuous variables will be

compared using the Student's t-test or Wilcoxon rank-sum test, as appropriate, and categorical variables will be compared using the chi-square test or Fisher's exact test, as appropriate. The time-to-event data will be compared between the groups using the log-rank test and the Cox regression analysis.

The one-sided α level of 0.05 was used for statistical significance for the primary hypothesis testing. The two-sided α level of 0.05 was used for all other analyses. Multiple comparisons will not be taken into account for statistical significance. All analyses will be conducted for the intention-to-treat population. We will compare the plastic stent and LAMS groups that participants are assigned to, regardless of whether they fully adhere to the study protocol. Outcomes will be summarised as medians (interquartile ranges) or mean ± standard deviations, as appropriate, for continuous variables and the number (percentage) of patients for categorical variables.

Interim analyses {21b}

There is no planned interim analysis.

Methods for additional analyses (e.g. subgroup analyses) {20b}

In each subgroup analysis of the clinical success stratified by clinically relevant parameters (e.g. the size, multiplicity, or extension areas of a pseudocyst, the duration from the onset of acute pancreatitis), we will compare the proportions of clinical success between the plastic stent and LAMS groups with a 90% confidence interval for a difference. We will assess the heterogeneity of treatment effect between subgroups by evaluating the Wald test on a cross-product of a specific subgroup-defining variable and the treatment group (plastic stent or LAMS) in the logistic regression model. Subgroups will be defined by organ failure(s) before randomisation (present vs. absent), institution, time from the onset of symptoms to randomisation (< 28 days vs. ≥ 28 days as a clinically plausible cut-off value for cyst wall maturation [1, 41], the size of pseudocyst (< 10 cm vs. ≥ 10 cm), sex (women vs. men), age (< 65 years vs. ≥ 65 years), a pseudocyst extension to the paracolic gutter (present vs. absent), an extension to the right side of the body (present vs. absent), an extension to the pelvis (present vs. absent), Charlson Comorbidity Index (< median vs. ≥ median), body mass index (< median vs. ≥ median), multiple endoscopic procedures (present vs. absent), percutaneous drainage (present vs. absent), a multilocular lesion (yes vs no), a biliary stricture, or duodenal obstruction (present vs. absent). Given the number of stratifying factors, the planned sample size may be relatively small to assess the effect modifications by those factors. Therefore, it should be noted that the secondary stratified analyses may not provide robust statistical assessments.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

In the primary analysis of clinical success, only cases where clinical success is confirmed according to the predefined criteria in the current trial will be treated as cases that meet the primary endpoint. Therefore, patients who are lost to follow-up within 180 days of the randomisation with no achievement of clinical success will be treated as cases with clinical failure. We will conduct a sensitivity analysis excluding those patients who are lost to follow-up and confirm that our findings do not change substantially. Cases with missing data on clinical success will also be treated as cases with clinical failure, but the proportion of these cases is assumed to be very low based on our clinical experiences. For cases with missing data on the covariates in the multivariable analyses, we will assign a major category for categorical covariates and a mean or median value, as appropriate, for continuous covariates. We will confirm that excluding cases with missing data does not alter our findings substantially.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The full protocol and statistical code will be accessible to the public upon reasonable request. The anonymised participant-level dataset will also be available upon reasonable request, but appropriate approval at each centre will be required. The results of the current trial will be presented at conferences/seminars and published in a peer-reviewed journal to maximise the chances of dissemination of the results to the public. The results will also be posted in the trial registries, ClinicalTrials.gov, University Hospital Medical Information Network (UMIN), and Japan Registry of Clinical Trials (jRCT).

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial steering committee consists of the principal investigator and the representative of the investigator team at each centre. The committee will hold an online meeting every 2–3 months to check the progress of the trial and share information on severe adverse events (SAEs). The Clinical Research Support Centre at The University of Tokyo Hospital provides organisational support for the current trial from the planning stage to the publication of the data (e.g. the monitoring of an annual report of the trial progress and SAEs submitted by the principal investigator).

Composition of the data monitoring committee, its role and reporting structure {21a}

An independent data and safety monitoring committee will not be formed for this trial.

Adverse event reporting and harms {22}

AEs are defined and graded by the American Society for Gastrointestinal Endoscopy lexicon guidelines [28] (definitions are described in Table 1). SAEs are defined as unfavourable events that cause patient death, life-threatening events, unexpected or prolonged hospitalisation, or permanent or severe disability, regardless of the plausibility of causal associations with the trial interventions. SAEs will be assessed and managed by the treating investigators at each centre. In the case of SAEs, the investigators will submit a report to the principal investigator using a pre-defined form. Subsequently, the principal investigator will consult with the IRB and the director of The University of Tokyo Hospital for the appropriateness of the trial continuation. The information on SAEs will be shared with all trial investigators to ensure the safety of the trial interventions.

Frequency and plans for auditing trial conduct {23}

No audit is planned in the WONDER-02 trial. The data will be monitored by the committee.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

We will submit any modifications of the protocol (e.g. changes to the eligibility criteria, participating centres, endpoints, and analyses) to the IRB at each centre and obtain approval. The information at the trial registries will be updated accordingly. Trial participants will be informed about the amendments approved by the IRBs.

Dissemination plans {31a}

The results of the WONDER-02 trial will be presented at conferences/seminars and published in a peer-reviewed journal to maximise the chances of dissemination of the results to healthcare professionals and the public and to contribute to improvements in public health. The results will also be posted in the trial registries, ClinicalTrials.gov, UMIN, and Japan Registry of Clinical Trials (jRCT). Plain language summaries of the findings will be shared with the participants upon request.

Discussion

The WONDER-02 trial has been designed as a multicentre RCT that aims to evaluate the non-inferiority of plastic stents to a LAMS in patients receiving EUS-guided drainage of pancreatic pseudocysts. There have been several clinical unmet needs in this field, and our survey of expert endoscopists and gastroenterologists demonstrated considerable heterogeneity in the clinical practice of endoscopic management of pseudocysts (unpublished data), suggesting an urgent need for RCTs for the standardisation of the treatment protocol in this setting. According to the increasing popularity of LAMSs in interventional EUS overall [42], we endoscopists may select this treatment modality without reasonable supporting evidence. Given the largely liquid contents of pseudocysts, the lesions are expected to be resolved without the need for a LAMS associated with high costs and specific adverse events. These lines of evidence motivated us to design and implement an RCT to investigate the non-inferior treatment efficacy of plastic stents compared to a LAMS in the management of pancreatic pseudocysts.

The WONDER-02 trial has specific strengths in addition to those of RCTs in general. First, the multicentre study design involving more than 20 centres will likely ensure the generalisability of our results. This strength is considerably important given the variations in clinical practice of endoscopic procedures, adjunctive treatment, and supportive treatment during the periprocedural period of EUS-guided treatment of PFCs [5, 43]. In addition, the relative rarity of patients with large-size pancreatic pseudocysts requiring interventions may be a hurdle for the timely enrolment of participants. To encourage enrolment, the current trial will be conducted at 26 centres (as of October 2023), and additional centres will be recruited considering the pace of the enrolment. During the past 5 years, there were 0.5–2 eligible cases per year at each participating centre (at least one case per year at a majority of centres). Therefore, the trial will be completed within the planned accrual period if three participants are enrolled at each centre during a 3-year study period, translating into the annual enrolment of approximately one participant per centre, which is quite feasible given the caseloads at the participating centres. Second, the broad inclusion criteria have been defined to ensure the representativeness of our participants as patients with pancreatic pseudocysts. Third, it may be technically difficult to place a plastic stent or LAMS in a targeted pseudocyst. The investigators involved in the trial interventions will be all endoscopists with sufficient expertise in EUS-guided interventions, and the technical success rate was reasonably high in our previous analysis [6]. Fourth, all participants will receive the trial interventions on an inpatient basis according to the local practice. The hospitalisation will allow us to evaluate adverse events and the timing of their occurrences accurately during the periprocedural period, not depending on the patient's self-report.

We acknowledge the potential challenges of the current trial. First, there may be difficulties in accurately differentiating pancreatic pseudocysts from other types of PFCs such as WON. Nonetheless, we have set up the online meeting platform so that we can hold the expert panel consisting of multiple gastroenterologists and board radiologists and make a decision on the eligibility in a timely fashion. Given the heterogeneous clinical courses by the aetiologies of pseudocysts (acute pancreatitis or others including postoperative PFCs), this factor will be included as an allocation factor during the randomisation process. Second, due to the nature of the interventions in the experimental and control groups, the participants and endoscopists cannot be blinded to the allocated groups.

The current clinical guidelines have no recommendation on the stent type used for EUS-guided drainage of pancreatic pseudocysts because no clinical RCTs have compared plastic stents and a LAMS in this setting. Therefore, the results of this large multicentre RCT are expected to serve as valuable evidence, which will help us to implement evidence-based practice for better clinical outcomes of patients with pseudocysts. Given that several endoscopists use plastic stents, but not LAMSs, in clinical practice due to a lack of experience in using a LAMS or the unavailability of the stent at their centres, our findings would propel the global trend of EUS-guided treatment of PFCs.

Trial status

The current version of the protocol is 1.0, which was updated on 16 August 2023. The recruitment started on 1 November 2023 and is scheduled to be completed on 1 September 2026.

Appendix

The list below describes the sites recruiting participants at the time of writing (25 October 2023) in alphabetical order.

1. Department of Gastroenterology, Aichi Medical University, Aichi, Japan

2. Department of Gastroenterology, Graduate School of Medicine, Chiba University, Chiba, Japan

3. Department of Gastroenterology, Gifu Municipal Hospital, Gifu, Japan

4. Department of Gastroenterology, Gifu Prefectural General Medical Center, Gifu, Japan

5. First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

6. Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Hokkaido, Japan

7. Division of Gastroenterology and Hepatobiliary and Pancreatic Diseases, Department of Internal Medicine, Hyogo Medical University, Hyogo, Japan

8. Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Tokyo, Japan

9. Department of Gastroenterology and Neurology, Kagawa University, Kagawa, Japan

10. Digestive and Life-style Diseases, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Japan

11. Department of Gastroenterology, Kameda Medical Center, Chiba, Japan

12. Department of Gastroenterological Endoscopy, Kanazawa Medical University, Ishikawa, Japan

13. Department of Gastroenterology and Hepatology, Faculty of Medicine, Kindai University, Osaka, Japan

14. Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan

15. Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

16. Department of Gastroenterology and Hepatology, Mie University Hospital, Mie, Japan

17. Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

18. Department of Gastroenterology and Hepatology, Okayama University Hospital, Okayama, Japan

19. Endoscopy Center, Osaka Medical and Pharmaceutical University Hospital, Osaka, Japan

20. Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University, Saitama, Japan

21. Department of Gastroenterology, St. Marianna University School of Medicine, Kanagawa, Japan

22. Department of Gastroenterology, Teikyo University Mizonokuchi Hospital, Kanagawa, Japan

23. Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

24. Third Department of Internal Medicine, University of Toyama, Toyama, Japan

25. Department of Gastroenterology, Wakayama Medical University School of Medicine, Wakayama, Japan

26. Department of Gastroenterology, Yamanashi Prefectural Central Hospital, Yamanashi, Japan

Abbreviations

AE	Adverse event
CT	Computed tomography
EUS	Endoscopic ultrasound
IRB	Institutional review board
LAMS	Lumen-apposing metal stent
PFC	Pancreatic fluid collection

RCT Randomised controlled trial
SAE Severe adverse event
WON Walled-off necrosis

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Authors' contributions {31b}
T.Sa., M.T., T.Iw., H.S., T.H., K.K., H.I., I.Y., and Y.N. contributed to the conception and design of the study. T.Sa. and Y.N. contributed to funding acquisition. T.Sa., T.H., and Y.N. wrote the original protocol. T.Sa., M.T., M.Ku., S.D., H.O., T.F., A.Mas., T.Iw., H.S., N.H., K.I., A.Mar., T.M., S.M., T.H., T.In., K.M., S.H., N.F., K.K., H.Ka., S.H., T.Sh., R.Y., H.Ko., K.N., T.O., M.Ki., I.Y., H.I., and Y.N. were responsible for trial data and management. T.Sa., T.H., K.K., and Y.N. developed the statistical analysis plan. T.Sa., T.H., and Y.N. wrote the paper. All authors reviewed and approved the paper.

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Availability of data and materials {29}
All investigators who participate in the WONDER-02 trial will have access to the final study dataset. The anonymised study data and statistical methods can be shared with the public by the primary investigator (Y.N.) upon reasonable request, but appropriate approval at the IRB may be required.

Declarations

Ethics approval and consent to participate {24}
The study protocol was approved by the centralised IRB at The University of Tokyo Hospital (Tokyo, Japan; #2023002P), and subsequently, the approved protocol was approved at the IRB at each collaborating centre. Written informed consent will be obtained from all potential participants. The study was designed and will be implemented according to the guidelines in the Helsinki Declaration [44]. The current protocol of the WONDER-02 trial is reported according to the SPIRIT reporting guidelines [45].

Consent for publication {32}
n/a. In the WONDER-02 trial, we do not plan to describe any details or use images/videos of an individual participant. In case that those data will be required for publication, written informed consent for the publication will be obtained from the corresponding participant. We will be willing to provide a model consent form upon reasonable request.

Competing interests {28}
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