BMJ Open

Prophylactic endoscopic sphincterotomy in patients unfit for cholecystectomy after an acute biliary pancreatitis episode (PROSECCO): study protocol for an open-label, two-armed, randomised controlled trial

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To cite: Tari E, Vincze Á, Czakó L, *et al*. Prophylactic endoscopic sphincterotomy in patients unfit for cholecystectomy after an acute biliary pancreatitis episode (PROSECCO): study protocol for an open-label, two-armed, randomised controlled trial. *BMJ Open* 2026;**16**:e114897. doi:10.1136/bmjopen-2025-114897

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-114897).

Received 04 December 2025
Accepted 07 April 2026

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ABSTRACT

Introduction Acute pancreatitis is a major cause of gastrointestinal admissions, with an overall mortality of approximately 3%, and 30–55% of cases are biliary in origin. After acute biliary pancreatitis (ABP), elderly or frail patients who are unfit for cholecystectomy remain at high risk of recurrent biliary events and related complications. However, the efficacy of prophylactic endoscopic sphincterotomy (ES) in this patient population remains unclear. Therefore, this study aims to evaluate whether performing prophylactic ES after ABP can reduce mortality and readmissions for biliary events in patients unfit for cholecystectomy.

Methods and analysis This prospective, multicentre, open-label randomised controlled trial will be conducted in Hungary, with planned international expansion, to assess the efficacy of prophylactic ES in patients with ABP unfit for cholecystectomy. 92 patients will be randomised 1:1 to prophylactic ES or conservative treatment. An interim analysis will be conducted after 65% of the planned enrolment or once 60 patients have completed 12 month follow-up or have experienced a primary outcome event, whichever occurs first. ES will be performed in accordance with current guidelines. Eligible participants are adults with a high probability of biliary aetiology but without a current indication for urgent endoscopic retrograde cholangiopancreatography (ERCP). The primary endpoint is time from randomisation to first recurrent pancreatobiliary event within 12 months, including recurrent ABP, cholangitis, choledocholithiasis requiring ERCP or pyogenic liver abscess. Secondary endpoints are pancreatobiliary-related and all-cause mortality, as well as events requiring intensive care. Follow-up visits will take place at 3, 6, 9 and 12 months post-discharge.

Ethics and dissemination This study protocol was approved by the Scientific and Research Ethics Committee of the Medical Council (NNGYK/34436-6/2025). The findings will be disseminated through presentation at scientific meetings and publication in a highly recognised, peer-reviewed international journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is designed as a prospective, randomised controlled trial, providing the highest level of evidence to evaluate prophylactic endoscopic sphincterotomy (ES) after acute biliary pancreatitis in frail patients unfit for surgery.
⇒ The multicentre design, with planned international expansion, enhances the generalisability of the findings.
⇒ Conducting the study in high-volume expert centres with fully trained endoscopists performing endoscopic retrograde cholangiopancreatography (ERCP) ensures high procedural quality.
⇒ The open-label design may introduce performance or assessment bias, despite the use of blinded statistical analysis.
⇒ The exclusive involvement of expert centres may reduce applicability to less experienced settings, and the relatively large required sample size in this frail patient population may complicate recruitment.

Trial registration number NCT07238296.

INTRODUCTION

Background

Acute pancreatitis (AP) is one of the leading gastrointestinal causes of acute hospital admissions, with an overall mortality rate of 3%.[1] In most Western countries, approximately 30–55% of the cases are caused by gallstones or sludge, referred to as biliary pancreatitis.[2] International guidelines recommend that in case of cholangitis or choledocholithiasis, an endoscopic retrograde cholangiopancreatography (ERCP) should be performed to clear the bile duct with endoscopic sphincterotomy

(ES).[3] After ERCP/ES is completed, the common bile duct is cleared, and the complications caused by the gallstones are significantly reduced.[4]

After acute biliary pancreatitis (ABP), patients remain at risk of recurrent episodes of biliary pancreatitis or other biliary events, such as acute cholecystitis, common bile duct (CBD) obstruction, cholangitis or biliary colic, associated with a high hospital readmission rate.[5]

Cholecystectomy is recommended after an ABP episode to prevent the recurrence of pancreaticobiliary events.[6]

However, some patients with gallbladder stones are elderly or frail and often have major medical problems, making them unsuitable candidates for surgery. It is still unclear whether prophylactic ES may prove beneficial in preventing the recurrence of ABP in these patients, despite the therapeutic procedure itself not being recommended by current guidelines.

In August 2023, we systematically searched for available studies in the literature. Cohort studies with relatively low sample sizes suggested the importance of ES in the study population.[7 8] However, no randomised controlled trials (RCTs) were identified comparing prophylactic ES with conservative treatment.

Objectives

This trial aims to generate grade-A evidence for the efficacy and safety of prophylactic ES in frail patients unfit for cholecystectomy after an ABP episode.[9 10]

It is hypothesised that patients undergoing prophylactic ES will experience fewer pancreatobiliary events and have lower mortality rates than those receiving conservative treatment during the 1-year follow-up period.

METHODS AND ANALYSIS

Trial design

We will conduct a prospective, multicentre, open-label, two-armed RCT with a superiority study design. Study participants will be randomly assigned to group A ('prophylactic ES') and group B ('conservative treatment') in a 1:1 ratio. Patient enrolment is planned to start in May 2026, with an anticipated study duration of 3 years.

The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement.[11]

Sample size

92 participants will be randomised to the intervention and conservative care arms (46 participants per arm). All eligible patients will be offered to participate in the study.

An interim analysis will be conducted after 65% of the planned enrolment or once 60 patients have completed the 12-month follow-up or have experienced an event described in the primary outcome, to reassess the sample size estimation and analyse the collected data.

Study setting

The leading centres will be the Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary.

Initially, the trial will be launched at two Hungarian centres (Institute of Pancreatic Diseases, Semmelweis University, Budapest; First Department of Medicine, Szent György Hospital, Székesfehérvár), after which additional centres will be invited to join. In all cases, the International Data Management Board will audit the centre and report to the Steering Committee (SC). The SC maintains the right to decide whether a centre meets the required quality requirements for joining the study.

Eligibility criteria

Inclusion criteria:

1. Adult patients (18 years and above).
2. Naïve papilla.
3. Evidence of AP based on the Atlanta criteria:
   - Pain in the upper abdomen.
   - Serum amylase or lipase concentration > 3 times the upper limit of normal.
   - Imaging features of acute pancreatitis on abdominal imaging.
4. High probability of a biliary aetiology defined by one or more of the following:
   - Gallstones or biliary sludge on any imaging modality.
   - Dilated common bile duct on imaging defined as >8 mm in patients ≤75 years or >10 mm in patients >75 years.
   - Abnormal liver enzymes (alanine aminotransferase (ALT) two times the upper limit of normal).
5. Patients unfit for surgery due to the attending physician's decision, eg, American Society of Anesthesiologists class ≥III; severe heart failure with reduced ejection fraction <40%, severe uncontrolled hypertension, chronic kidney disease stage four or five.

Exclusion criteria:

1. Previous cholecystectomy.
2. Previous ES or pancreatobiliary stenting.
3. Indication of urgent ERCP/ES as recommended by the guidelines.[3]
   - Signs of cholangitis.
   - Presence of a CBD stone on any imaging modality.
   - Signs of a stone on endoscopic ultrasonography or magnetic resonance imaging in the presence of either abnormal liver enzymes (persistently elevated ALT and aspartate aminotransferase with less than a 20% decrease over four days) or a dilated CBD (defined as above).
4. Chronic pancreatitis.
5. Estimated life expectancy <12 months.
6. ERCP is contraindicated, eg, the procedure cannot be carried out safely due to the patient's comorbidities or physical status; high risk of bleeding or contraindication of the discontinuation of the anticoagulation therapy.

7. ERCP is technically not feasible due to altered anatomy, eg, total gastrectomy, Roux-en-Y gastric bypass anatomy.
8. Pancreatobiliary malignancy.

Interventions

Papillary cannulation and sphincterotomy techniques will be performed in adherence to the recommendations outlined in the European Society of Gastrointestinal Endoscopy (ESGE) guideline.[12]

All recommended measures for post-ERCP pancreatitis prevention must be implemented, including the use of prophylactic pancreatic stents, rectal non-steroidal anti-inflammatory drugs (NSAIDs) and optimal hydration protocols where appropriate.

All rescue techniques may be utilised if necessary, in accordance with clinical judgement and guideline recommendations.

ERCP/ES will be performed by endoscopists with experience of >300 ERCP procedures and a native papilla cannulation success rate of at least 90%.

If the ES cannot be performed during the initial ERCP, the number of further attempts is under the discretion of the endoscopist.

The conservative treatment arm will receive standard non-interventional management without any endoscopic procedure.

Outcomes

Primary outcome

The primary outcome is a composite endpoint defined as the time from randomisation to the first recurrent pancreatobiliary event within 12 months, including any of the following:

- Cholangitis (according to the Tokyo guidelines).
- Recurrent ABP—defined as above.
- Choledocholithiasis.
- Cholangiogenic liver abscess.

Secondary outcomes

The following outcomes will be assessed at 3, 6, 9 and 12 months:

- Occurrence of the individual endpoints of the composite primary outcome.
- Number of pancreatobiliary events requiring intensive care unit admission.
- Occurrence of mortality associated with pancreatobiliary events.
- Occurrence of all-cause mortality.
- Post-ERCP pancreatitis, with a focus on moderate or severe cases.
- Occurrence of other post-ERCP complications, including bleeding, cholangitis and perforation.
- Occurrence of acute cholecystitis—Tokyo guidelines.
- Length of hospitalisation, defined as days between admission and the first day of medical fitness for discharge.

Participant timeline

An attending physician will inform the patients about the trial in detail, and participants must complete a written informed consent (see online supplemental material).

Before randomisation, all patients must undergo imaging (eg, ultrasound or computed tomography scan).

Randomisation will occur after the acute pancreatitis episode has improved, as indicated by reduced abdominal pain and a sustained decrease in inflammatory markers for at least 48 hours.[13]

On the intervention arm, prophylactic ES will be carried out during the index admission for the acute biliary pancreatic episode.

The patient or their representative will be asked to record all biliary events during the follow-up period and will be contacted on the phone at 3, 6, 9 and 12 months after discharge to collect information. All reported events will be verified through medical record review and available electronic health records, as detailed in the Data collection and management section.

At the patient level, the study will end 12 months after discharge or if any automatic dropout criterion is met.

Additional data collected at baseline

Additional data on demographics, comorbidities and medical history, especially focusing on previous biliary events, will be collected.

The reason for deeming a patient unfit for surgery will be documented.

Randomisation

Patients will be randomised in a 1:1 ratio to group A ('prophylactic ES') or group B ('conservative treatment') using block randomisation with randomly varying block sizes, stratified by participating centre and patient gender. The allocation sequence will be generated by an independent statistician in R (≥4.50.2) using the randomizeR package (≥3.00.2).[14] Allocation concealment will be ensured through a centralised, secure, web-based electronic clinical data management system (ECDMS) with role-based access, where treatment allocation is revealed only after patient enrolment.

Blinding

Due to the nature of the intervention, blinding of participants and care providers is not feasible, and no sham procedure will be performed. Allocation concealment will be maintained until randomisation. Outcome assessors and statisticians will be blinded to group allocation where feasible and will receive anonymised data for analysis.

Data collection and management

Data will be collected and managed using a centralised, secure, web-based ECDMS. Study data will be entered into electronic case report forms within the system by trained local investigators. Follow-up will be conducted through questionnaires and medical record reviews to verify reported clinical events. To minimise loss to follow-up, multiple contact attempts will be made, and additional

contact details (eg, caregivers or primary care physicians) will be collected at baseline. Each participant will receive a unique identification number. Personal identifiers will be stored separately from clinical data and will only be accessible to personnel directly involved in the trial. Data completeness and consistency will be ensured by the Chief Investigator, who will oversee the dataset's quality and reliability. Incomplete or inconsistent entries will generate data queries for the local investigators.

Statistical analysis plan

All analyses will be performed using R (version ≥4.50.0; R Core Team, 2025) with appropriate packages. A two-sided α of 0.05 will be considered statistically significant unless otherwise noted. Confidence intervals (CIs) will be reported at the 95% level.

Analysis populations:

- Intention-to-treat (ITT): All randomised patients, regardless of received treatment or adherence.
- Per-protocol (PP): Subset of ITT excluding major protocol deviations.
- Safety set: All randomised patients who received the intervention or conservative treatment.

The primary analysis will follow the ITT principle; PP analyses will be conducted as sensitivity checks.

Descriptive analyses

Continuous data will be summarised as n, mean±SD, median (IQR); categorical data as n (%). Time-to-event data will be summarised with Kaplan-Meier curves and median survival (95% CI), where feasible (ie, when 5+events were observed and median survival was reached). Incidence rates will also be reported.

Primary outcome

The primary composite endpoint is the time from randomisation to the first recurrent pancreatobiliary event within 12 months (recurrent ABP, cholangitis, choledocholithiasis requiring ERCP or cholangiogenic liver abscess).

- Model: Cox proportional hazards regression, estimating the HR for prophylactic ES vs conservative treatment.
- Covariates: Centre (stratification factor), sex.
- Assumptions: The proportional hazards assumption will be tested using Schoenfeld residuals. If violated, time-varying effects, stratified analyses or other methods will be considered.
- In case <10 events are observed: The Cox model may be reduced or changed to a Kaplan-Meier/log-rank test or other appropriate statistical method.
- In case of convergence issues: the 'Centre' term may be dropped.

Secondary outcomes

- Individual components of the composite endpoint: Separate Cox models.
- All-cause mortality and pancreatobiliary-related mortality within 12 months: Cox regression (or Kaplan-Meier/log-rank if <10 events).
- Pancreatobiliary events requiring ICU admission: Cox regression or log-rank as above.
- Post-ERCP complications (pancreatitis, bleeding, cholangitis, perforation) and the occurrence of acute cholecystitis: Incidence rates and risk differences with 95% CIs will be reported.
- Length of hospitalisation: Compared between arms using the Wilcoxon rank-sum test or linear regression if assumptions hold. If >10% of one arm is lost to follow-up or discontinued during the initial hospitalisation, survival-based methods may be used.

Interim analysis

An interim analysis will be conducted after ~65% of the target sample has completed a 12-month follow-up or experienced an event relevant to the primary outcome (≈60 patients). The timing of the interim analysis (expressed as % of the target sample) may be adjusted at the Investigators' and the Data Monitoring Committee (DMC)'s discretion in accordance with the chosen framework.

- Framework: Hwang-Shih-DeCani alpha-spending (γ=−0.5).
- Boundaries: Critical p=0.0296 at interim; p=0.0334 at final analysis for 65% of the target sample; would be recalculated if the actual number of patients differ.
- Decisions: The DMC may recommend early termination for clear efficacy or futility after the results of the interim analyses become available.
- Following the interim analysis:
  - Enrollment/follow-up may continue.
  - The database will be cleaned (reconciled) and locked.
  - The critical confidence level will be calculated and the primary efficacy analysis will be completed.
  - The DMC will review the results and decide whether to continue, modify, or terminate the trial for efficacy or lack of efficacy.
  - In case the trial is stopped for efficacy, all remaining pre-specified analyses will be performed.
  - The sample size may be recalculated at the interim stage (unblinded reassessment, conditional power).

Handling of missing data

- Time-to-event outcomes: Patients lost to follow-up will be right-censored at last contact.
- Binary or continuous outcomes: Analyses will use observed data only; no imputation is planned.

Sensitivity analyses

PP analyses will also be reported if the results between the PP and the ITT populations differ meaningfully.

The safety-type endpoints will be rerun using the Safety Population if the Safety and the ITT populations should differ.

As a sensitivity analysis for the primary time-to-event outcome, patients lost to follow-up will be treated as event-free until the end of the study. This represents an extreme scenario of non-informative censoring in the favourable direction and allows quantification of the maximum possible impact of loss to follow-up on the estimated HR. If the primary conclusion is unchanged under this assumption, it provides evidence of robustness against informative censoring.

Multiplicity

No formal adjustment for multiplicity will be applied. The trial has a single pre-specified primary endpoint; secondary endpoints will be considered exploratory and interpreted descriptively, with nominal p values reported without alpha adjustment.

Sample size determination

According to a recent meta-analysis, the risk of recurrent pancreatitis after a first episode of ABP was 11.9%, decreasing to 6.6% in patients undergoing cholecystectomy.[15] In a prospective cohort study by Uomo *et al*, patients unfit for surgery who underwent ES had a 5% recurrence rate over 2 years (5). Assuming a similar protective effect of ES as cholecystectomy, we estimated a 5% incidence of recurrent pancreatobiliary events in the intervention arm.

In contrast, studies have reported recurrence rates between 18% and 61% in conservatively treated patients awaiting cholecystectomy. For the present study, we therefore assumed a 30% incidence of recurrent pancreatobiliary events in the control arm during the 12-month follow-up period, derived from both the published literature and our review of institutional case records.[16]

Based on these assumptions, and allowing for a 25% dropout rate, a total of 92 patients (46 per arm) are required to achieve 80% power at a two-sided 5% significance level. Sample size was determined via a Monte Carlo simulation: each iteration generated survival data under flexible nonparametric baseline hazards and evaluated the treatment effect using a Cox proportional hazards model. An interim analysis will be conducted after 65% of the planned enrolment (≈60 patients with 12-month follow-up), applying the Hwang-Shih-DeCani alpha-spending function with adjusted significance thresholds (p=0.0296 at the interim analysis, p=0.0334 at the final analysis).

Safety and adverse events

In case of a recurrent biliary event requiring ERCP after randomisation, the procedure will be performed promptly in both study arms according to clinical indications. (2) All necessary measures should be taken to prevent the post-ERCP adverse events. (3) A safety analysis will be performed after the first 20 patients have completed a 3-month follow-up. The results will be reviewed by the SC. Both the overall safety profile and the ERCP complication rate will be evaluated; if the complication rate is below 10%, the procedure will be considered safe in the study population.

Withdrawal from study

Investigators may submit a recommendation for excluding a participant from the per-protocol analysis. All such requests will be documented. Based on the available information, the SC may decide to exclude the patient from the per-protocol population if the protocol deviation is directly related to the intervention or is expected to influence the primary or secondary outcomes.

Automatic withdrawal from the study will occur in the following cases: (1) withdrawal of consent at any time; (2) inability to contact the patient or inability to obtain essential follow-up data from electronic medical records.

The DMC will evaluate trial-level safety data and may recommend continuation, protocol modification or early termination of the trial based on safety considerations or other emerging evidence.

Ethical and dissemination

Ethical approval and trial registration

The trial is registered at ClinicalTrials.gov (NCT07238296).

The protocol has been approved by the Scientific and Research Ethics Committee of the Medical Council (NNGYK/34436-6/2025).

The study will be performed following the declaration of Helsinki and the International Conference on Harmonisation and Good Clinical Practice guidelines.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this study. Given the frailty and advanced age that commonly characterise the target population, patient and public involvement was not considered feasible. Nevertheless, the study procedures were designed to reflect real-world clinical practice in this high-risk group. Further details are provided in the Methods and analysis section.

Trial organisation

The guarantor of the trial is the Institute of Pancreatic Diseases, Semmelweis University, Budapest, Hungary. The following committees and boards will be involved:

The SC will be led by BE (gastroenterologist, internal medicine specialist); the members will be ÁV, LC, ET and PH. The SC will decide on all relevant questions, including dropouts during the study.

International Translational Advisory Board (ITAB): The board will consist of VS, SBL, MB and SC. The ITAB will continuously monitor the progress of the study and will advise the SC.

The study was designed by the SC and ITAB.

Data Monitoring Committee (DMC): DMC will oversee patient safety, study conduct and accumulated outcome data. The DMC will review adverse events, monitor the interim analysis and advise the SC on whether the trial should continue, be modified or be stopped. Members

of the DMC will be appointed prior to the initiation of patient enrolment.

Planned start date: 1 May 2026.

Anticipated study duration: 3 years

DISCUSSION

Our study is designed to determine whether a prophylactic ES, after ABP, leads to a reduction of mortality and readmissions for biliary events in patients with ABP unfit for cholecystectomy.

If an ES proves superior to the conservative treatment in the study population, it could be recommended routinely and incorporated into the guidelines, reducing the risk of recurring biliary events.

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Contributors ET and BE conceived the study and developed the study design. ET drafted the manuscript. BE supervised the project and critically revised the manuscript for important intellectual content. MK contributed to the statistical design and methodology of the study. ÁV, LC, VS, SBL, SC, MB, PH and MK contributed to the development of the study concept, provided clinical expertise and critically revised the manuscript. BE acted as the guarantor. All authors read and approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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