BMJ Open

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025551
Article Type:	Protocol
Date Submitted by the Author:	01-Aug-2018
Complete List of Authors:	Kucserik, Levente; Universitatea de Medicina si Farmacie din Targu Mures, Division of Surgery Márta, Katalin; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine; János Szentágothai Research Center, University of Pécs Kelemen, Dezső; Pecsi Tudomanyegyetem, Surgery Clinic Vincze, Áron; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Division of Gastroenterology, First Department of Internal Medicine; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine Lázár, György; University of Szeged, Department of Surgery Czakó, László; University of Szeged, First Department of Medicine Szentkereszty, Zsolt; University of Debrecen, Department for Surgery Papp, Maria; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Palatka, Károly; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Izbéki, Ferenc; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Divison of Gastroenterology Altorjay, Áron; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Division of Surgery Török, Imola; Universitatea de Medicina si Farmacie din Targu Mures, Division of Gastroenterology Barbu, Sorin; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Tantau, Marcel; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Vereczkei, András; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department for Surgery Bogár, Lajos; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department of Anaesthesiology and Intensive Therapy Dénes, Márton; County Hospital Targu Mures Szentesi, Andrea; Pecsi Tudomanyegyetem, Institute for Translational Medicine; Szegedi Tudomanyegyetem, MTA-SZTE Translational Gastroenterology Research Group Lerch, Markus; Universitatsmedizin Greifswald, Department of Medicine A Neoptolemos, John; University of Heidelberg Sahin-Toth, Miklos; Boston University Petersen, Ole; Cardiff University, Medical Research Council Group Hegyi, Péter; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar,

	Institute for Translational Medicine; MTA-SZTE Translational Gastroenterology Research Group
Keywords:	acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Levente-Pál Kucserik MD[1], Katalin Márta MD[2,3], Áron Vincze MD PhD[2,4], György Lázár MD PhD DSc[5], László Czakó MD PhD DSc[6], Zsolt Szentkereszty MD PhD[7], Mária Papp MD PhD[8], Károly Palatka MD PhD[8], Ferenc Izbéki MD PhD DSc[9], Áron Altorjay MD PhD DSc[10], Imola Török MD[11], Sorin Barbu MD PhD[12], Marcel Tantau MD PhD[12], András Vereczkei MD PhD DSc[13], Lajos Bogár MD PhD DSc[14], Márton Dénes MD[15], Andrea Szentesi PhD[2], Markus Lerch MD PhD DSc[16], John Neoptolemos MD PhD DSc[17], Miklos Sahin-Tóth MD PhD DSc[18], Ole Petersen MD PhD DSc[19], Dezső Kelemen* MD PhD[13], Péter Hegyi* MD PhD DSc[2,20].

1 Division of Surgery, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
2 Insitute for Translational Medicine, University of Pécs Medical School, Pécs, HU
3 János Szentágothai Research Center, University of Pécs, Pécs, HU
4 Division of Gastroenterology,First Department of Internal Medicine, University of Pécs Medical School, Pécs, HU
5 Department of Surgery, University of Szeged, Szeged, HU
6 First Department of Medicine, University of Szeged, Szeged, HU
7 Department for Surgery, University of Debrecen, Debrecen, HU
8 Division of Gastroenterology, University of Debrecen, Debrecen, HU
9 Divison of Gastroenterology, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehlrvár, HU
10 Divison of Surgery, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehérvár, HU
11 Division of Gastroenterology, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
12 Division of Gastroenterology, Universitatea de Medicina si Farmacie din Cluj Napoca, Cluj Napoca, RO
Tantau, Marcel; Universitatea de Medicina si Farmacie din Cluj Napoca
13 Surgery Clinic, University of Pécs, Pécs, HU
14 Department of Anaesthesiology and Intensive Therapy, University of Pécs Medical School, Pécs, HU
15 County Hospital Targu Mures, Targu Mures, Ro
16 Department of Medicine A, University Medicine Greifswald, Germany
17 Department of Molecular and Clinical Cancer Medicine, University of Liverpool,
Liverpool, UK
18 Center for Exocrine Disorders, Department of Molecular and Cell Biology, Boston, USA; University Henry M. Goldman School of Dental Medicine, Boston, Massachusetts, USA
19 Medical Research Council Group, Cardiff School of Biosciences, Cardiff University,
Cardiff, CF10 3AX, Wales, UK
20 Hungarian Academy of Sciences - University of Szeged, Translational Multidisciplinary Research Group, Szeged, Hungary

*: equally contributed

E-mail addresses of the authors:

LK k.levente.p@gmail.com, DK kelemende@gmail.com, AV vereczkei.andrás@pte.hu, IT torokimola@gmail.com, ÁV vincze.aron@pte.hu, GyL lazar.gyorgy@med.u-szeged.hu, LC czako.laszlo@med.u-szeged.hu, ZsSz szentkerzs@freemail.hu, MP papp.maria@med.unideb.hu, KP palatka@med.unideb.hu, FI fizbeki@gmail.com, ÁA altorjay@mail.fmkorhaz.hu, SB barbu@pancreasclub.ro, MD denesmatyi@yahoo.com, LB bogar.lajos@pte.hu, MT matantau@gmail.com, KM katalin.martak@gmail.com, ASz szentesiai@gmail.com, JN jneoptolemos1@gmail.com, MM lerch@uni-greifswald.de, MST miklos@bu.edu, OP PetersenOH@cardiff.ac.uk, PH hegyi2009@gmail.com

Corresponding Investigator: Péter Hegyi MD, PhD, DSc

Phone: +(36-70) 375-1031

e-mail: hegyi.peter@pte.hu, p.hegyi@tm-pte.org

Coordinating institution: University of Pecs – Medical School

Institute for Translational Medicine

12 Szigeti Street, PÉCS, H-7624, HUNGARY

FAX: +(36-72) 536-247

Phone: +(36-72) 536-246

web: www.tm-pte.org

ABSTRACT

Introduction. According to the literature, early cholecystectomy is necessary to avoid complications related to gallstones after an initial episode of acute biliary pancreatitis (ABP). A randomized, controlled multicenter trial (the PONCHO trial) revealed that in the case of gallstone-induced pancreatitis, early cholecystectomy was safe in patients with mild gallstone pancreatitis and reduced the risk of recurrent gallstone-related complications, as compared with interval cholecystectomy. We hypothesize that carrying out a sphincterotomy (ES) early after ABP allows us to delay cholecystectomy, thus making it logistically easier to perform and potentially increasing the efficacy and safety of the procedure.

Methods/Design. EMILY is a prospective, randomized, controlled multicenter trial. The patients are randomized to two groups: (1) early cholecystectomy (within 6 days after ES) and (2) patients with delayed (interval) cholecystectomy (between 45 and 60 days after ES). During a 12-month period, 89 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (that is, recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The secondary endpoints are organ failure, biliary leakage, technical difficulty of the cholecystectomy, surgical and other complications.

Discussion. In the EMILY trial, the planned target is to show that the risk of biliary events will not be increased in case of endoscopic sphincterotomy combined with delayed cholecystectomy, compared to early cholecystectomy.

Ethics and dissemanitaion. The trial has been registered at the ISRCTN (ref no. 35066) and approved by the relevant organisation, the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Keywords: acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

ARTICLE SUMMARY

EMILY is a prospective, randomized-controlled, multicenter trial aiming to show that the risk of biliary events will not be increased in case of ES combined with delayed cholecystectomy, compared to early cholecystectomy. This trial provides the first evidence concerning the possible benefits of ES on timing cholecystectomy. All patients with mild ABP will have the possibility to take part in the trial.

Strengths and limitation

Strength 1: The study is designed to achieve conclusion on the highest evidence level including (i) multinational (ii) multicentric approach, (iii) international trial registration and (iv) publication of the pre-study protocol

Strength 2: Only high volume, expert centers can join to the study. They have to provide (i) laparoscopically trained surgeons with >100 laparoscopic procedures performed and (ii) ERCP/ES trained gastroenterologist with >50 ES completed within a year.

Strength 3: The study enjoys continuous support from (i) an International Translational Advisory Board (ITAB) including top, well-established experts from different are of research field (ii) an Independent Data Management Board (IDMB).

Strength 4: The final conclusion can be achieved with low number of patients within a relatively short period.

Limitation 1: The study will provide no evidence concerning the usefulness of ES in moderate and severe ABP.

INTRODUCTION

Acute pancreatitis is one of the leading gastrointestinal causes of acute hospital admissions [1, 2]. In most cases, it is caused by gallstones, sludge or edema [3]. Gallstone-induced pancreatitis involves a pathophysiologic factor, namely a distal common channel of the biliary and pancreatic ducts, which can be found in 80% of acute biliary pancreatitis (ABP) [4]. Acute biliary pancreatitis is a clinical entity with high rates of morbidity (15–50%) and mortality (20–35%) [5]. After ABP, several complications may occur; recurrent acute pancreatitis, cholestasis and fistula affecting the hepatobiliary system or other biliary events, such as acute cholecystitis, obstruction of the common biliary duct, cholangitis or biliary colic [6, 7]. Interval cholecystectomy after mild ABP is associated with a high risk of readmission for recurrent biliary events, especially after recurrent ABP [8]. The international practice guidelines recommend that in case of cholangitis or choledocholithiasis an ERCP should be performed to clear the bile duct with endoscopic sphincterotomy (ES). In addition, cholecystectomy should also be performed to avoid complications related to recurrent biliary events [9, 10]. In patients with clinically severe pancreatitis, with local complications, such as pancreatic necrosis or organ failure, the intervention namely the laparoscopic cholecystectomy (LC) is delayed 6 months until complications are resolved [11]. In cases of mild ABP, cholecystectomy is recommended between days 7 and 21 [4]. The latest studies show that after discharge of patients with ABP, cholecystectomy could reduce the risk of a recurrent ABP and other gallstone-induced complications [12]. In this setting, surgeons still prefer delayed cholecystectomy for efficacy and safety and for logistical reasons [13]. Some publications draw attention to ERCP/ES, which could reduce mortality and the formation of severe biliary complications [3, 14]. The aim of the EMILY trial is to combine a surgical treatment and a

gastroenterological procedure to investigate if ES with delayed cholecystectomy (within 45 to 60 days after ES) compared with ES with early cholecystectomy (within 5 to 6 days after ES) could reduce recurrent biliary events.

METHODS

Design: EMILY is a prospective, randomized-controlled, multicenter trial. The patients are randomized to two groups: (1) Patients who undergo early cholecystectomy (within 6 days after ES) and (2) patients who undergo delayed (interval) cholecystectomy (between 45 and 60 days after ES). During a 12-month period, 89 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic and cholangitis). The secondary endpoints are: organ failure, biliary leakage, technical difficulty of cholecystectomy, and surgical and other complications.

This study was structured following the SPIRIT 2013 [15] guideline defining standard protocol items for clinical trials and got the relevant ethical approval EKU/2018/12176-5 (Scientific and Research Ethical Committee, Medical Research Council, Hungary).

Trial organization, committees and boards: The coordinator and designer of the EMILY study is the Centre for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Pancreatic Study Group (HPSG-coordinating society, www.pancreas.hu). The HPSG was established in 2011 to stimulate research in pancreatic diseases.

Until now, it has launched three international observational clinical studies in 2014 [16-18] (EASY, APPLE and PINEAPPLE) and two interventional studies (PREPAST [19] – 2014 and GOULASH [20] – 2017) and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [21-24].

The following committees and boards will be involved: Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist).

The members in Szeged (HU) will be: LC (gastroenterologist), GL (surgeon); Debrecen (HU): MP (gastroenterologist), KP (gastroenterologist), ZS (surgeon); Pécs (HU): ÁV (gastroenterologist), DK (surgeon); Székesfehérvár (HU): FI (gastroenterologist), ÁA (surgeon); Targu Mures (RO): IT (gastroenterologist), LK (surgeon); Cluj Napoca (RO): BS (gastroenterologist), TM (surgeon). KM is a trial management specialist, whereas AS leads the multidisciplinary core facility which will assist the scientists to run the study successfully. The SC will make decisions concerning all relevant questions including drop outs during the study.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

The study was designed by the SC and ITAB. It was funded by the University of Pécs, Medical School. The sponsor was not involved in the design of the study, and will have no access to database or the randomization code.

The study also contains an independent physician and safety manager as required by the ethical regulation.

Study population: All patients with mild ABP will be informed of the possibility to take part in the EMILY trial. After the consent form is signed participants will be randomized to 2 groups if they meet all the inclusion and no exclusion criteria (*Figure 1*).

Inclusion criteria: The criteria for inclusion in the study: (1) patients older than 18 years of age; (2) diagnosis of acute pancreatitis (at least 2 of the following 3 symptoms: upper abdominal pain, serum lipase or amylase is three times higher than the upper limit of normal and characteristic findings for acute pancreatitis on imaging); (3) the presence of ABP (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST; (4) mild ABP (meaning no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present; (5) ERCP/ES during the present ABP without complication; and (6) signed written informed consent (all included patient will sign the consent which contains the information about the trial and procedures) *(Figure 1)*.

Exclusion criteria: A patient's bad physical status can be an exclusion criterion. American Society of Anesthesiologists (ASA) III patients >75 years old; ASA IV or V patients, will be excluded. Patients with continuous alcohol abuse, acute or chronic cholecystitis during hospitalization, chronic pancreatitis, pregnancy, previous ES or cholecystectomy will also be excluded *(Figure 1)*.

Time of randomization: 5 criteria are described by the PONCHO trial [25]. If these 5 criteria are met, the informed consent will be signed by the patient and a control abdominal CT will be carried out before discharge. The patient can then be randomized. These criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged; (2) no need for opioid analgesics; (3) declining C-reactive protein levels and <100 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) resumed oral intake on the part of the patient.

Randomization: Randomization should be done as described above. The patient can be randomized by the study coordinator using a randomization module with sealed envelope. Patient data will be uploaded with the help of the administrator to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy *(Figure 1)*.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

Blinding: In prevention of patient's selection to group A and B trial participants, care providers and outcome assessors will be blinded until the allocation, as no access to randomization sequence. From assignment to intervention blinding cannot be provided considering the study characteristics (exact date of cholecystectomy). The allocation sequence is unblinded only to data analysts who are completely independent form medical team (decision making) and data collection.

Endpoints

Primary endpoint. The primary endpoint is a composite endpoint, which is based on mortality and on recurrent biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The observation period is three months. We decide based on criteria in *Figure 2* if a complication is present or not.

Secondary endpoints. We hypothesize that cholecystectomy for ABP between days 45-60 after discharge in patients with ES is as effective and safe as early cholecystectomy (within 6 day after ES). In order to evaluate this, we will observe the following parameters: the number of biliary colic registered for the patient, difficulty of cholecystectomy (on a scale of 0-10, 0=easy, 5=moderately difficult, 10=hard, rate of conversion to open cholecystectomy, total length of hospital stay, need for ICU admission and total length of ICU stay, organ failure and biliary leakage *(Figure 2)*.

Treatment protocol

Randomization: Group A. Early cholecystectomy

Group B. Delayed cholecystectomy

We randomize patients into two groups after ES *(Figure 3):*

Group A: The patient is randomized to the early cholecystectomy group, and cholecystectomy will be performed within 6 days after ES.

Group B: The patient is randomized to the delayed cholecystectomy group, and the cholecystectomy will be carried out between 45 to 60 days.

Discontinuing or the modification of the allocated interventions for a trial participant is based on surgical causes like contraindicated opus, need for convertion to open cholecystectomy, or when the patient does not present to the hospital for cholecystectomy. Switching over the two interventions is not possible considering the trial characteristics, however in case of acute cholecystitis acute cholecystectomia can be performed independently from this trial. The case must be presented to SC.

Surgical details and quality control: ERCP/ES will be performed according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [26] and the laparoscopic cholecystectomy will follow the European Association Guidelines for Endoscopic Surgery [27]. The patients will be operated on by laparoscopically trained surgeons with >100 laparoscopic procedures performed and by an ERCP/ES trained gastroenterologist with >50 endoscopic sphincterotomies completed within a year. Centers which intend to randomize at least 15 patients and are able to perform an early cholecystectomy and ERCP/ES are

eligible to participate in the study. ES data will then be collected on the incidence of choledocholithiasis, percentage bile duct injury, duration, and perceived difficulty (on a scale of 0-10).

Diagnosing and treating ABP: In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct.

Data collection and follow-up: Data will be collected in a personalized database, and follow-up will consist of questionnaires *(supplementary figure 1)*. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within 90 days after ES to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator.

The personal information about enrolled participants will only be shared with IDMB as uploaded data for randomization, after data analysis only randomization code will be used for identification to protect confidentiality during, and after the trial. Only the principal investigator and the IDMB will have access to the final trial dataset. However only identification code is used, we can aside from duplicated patient's data as cholecystectomy can not be performed twice.

Sample size estimation method

Primary endpoint: a composite of gallstone-related complications or mortality occurring within 6 months after randomization

Hypothesis: With regard to our hypothesis, based on an equivalence (non-inferiority) trial, we found no difference between the two groups (5%) in mortality or readmission for gallstone-related complications within 3 months after randomization.

Starting point: Considering the results of the PONCHO trial involving 264 patients, where a subgroup of 77 patients underwent endoscopic sphincterotomy: the primary endpoint occurred for 1 subject in the same-admission cholecystectomy group (3%) and 7 subjects in the interval admission group (17%). The difference between the two groups was not significant at the 5% level (p=0.07). The results for the current sample size estimation were reached using the difference between the two proportions above (14%) calculated with a 5% drop-out rate. They are listed in the table below *(Figure 4):*

Data management and statistical analyses: Data will be handled by an independent Clinical Research Organizer. Electronic CRF (eCRF) will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager according to a Data Cleaning Plan (DCP). Adverse events will be coded using MedDRA according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements.

Safety Analysis Set (SAS, all patients enrolled in the study), Per Protocol Set (PPS, all enrolled patients who finished the study conforming to the requirements of the study protocol) and Intention to Treat (ITT, all randomised participants who start on a treatment, excluding consent withdrawals) will be performed.

Baseline patient and disease characteristics will be analysed using descriptive analysis. Demographic and baseline characteristics will be summarised for the overall study population. Descriptive statistics for both the primary and secondary parameters will be analysed similarly.

Subgroup analyses will be perform concerning the imaging alterations (1: no gallstones or sludge on imaging, 2) sludge or 3) gallstone).

In case of important protocol modifications IDMB will report to the SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm

Premature termination of the study: In the interests of patient safety, an interim analysis will be conducted after 15 patients and after half of the presumed number of patients (45) have completed the study. IDMB will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subjects' right, safety and well-being and to guarantee the plausibility of clinical data. Similarity of groups at baseline will be also checked. The study will also be stopped if the two groups' results differ significantly ($p<0.001$). The study will be discontinued if the difference between the planned number of patients and the actual number is higher than 60% within one year. IDMB will report to SC.

Centers: The trial will be launched in four Hungarian (Szeged, Debrecen, Pécs and Székesfehérvár) and two Romanian centres (Targu Mures and Cluj Napoca), after which the study will be open to other centres. In all cases, the IDMB will conduct an audit of the center and will report to the SC. The SC maintains the right to decide whether a center meets the required quality to join the study.

The full protocol will we available for public in an open access journal.

Publication policy: We would like to publish the results in one of the internationally highly recognized decent journals**.** Centers providing more than 25 patients can provide 4 authors to the authorship list: 2 surgeons and 2 gastroenterologists.

Patient and Public Involvement: This pre-study protocol contains no results and data, therefore patients and or public were not involved.

DISCUSSION

In the case of early laparoscopic cholecystectomy, while dissection and logistics are more difficult [6, 7] compared with delayed (interval) cholecystectomy, it is still more effective. Delayed cholecystectomy in a mild form of ABP is preferred by many surgeons, but a number of complications can occur: recurrent ABP, acute cholecystitis, obstruction of ductus choledochus, and uncomplicated biliary colic [6, 7]. After ERCP/ES is performed, the common bile duct is cleared, the complications caused by

gallstones or sludge are significantly reduced [28]. The EMILY study is designed to determine if ERCP/ES for mild ABP aids in delaying the cholecystectomy to day 45-60 after discharge among patients with ABP.

If an ES aids in delaying a cholecystectomy, then we can reduce early cholecystectomy-related complications and the surgeons can proceed with a safer, easier cholecystectomy using this method of treatment.

ACKNOWLEDGEMENTS

Funding: Center costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs-Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patients life with research activities like registries, observational and interventional trial organizations (https://tm-centre.org).

There are no financial and other competing interests for principal investigators (LK, DK), included patients or any member of the trial.

ETHICS AND DISSEMINATION

Trial registration: The trial has been registered at the ISRCTN (reference number 35066).

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Protocol Version: V1.0 10.07.2018.

Start of the patient recruitment: In September, 2018.

Additional information and future plan: Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will give informed consent. The samples will be stored at -80^{o}C.

The post-trial care will follow the routine tratment protocols. In case if patient suffer a harm during hospitalization all of the responsability is taken by the hospital where the patient is treated.

AUTHORS' CONTRIBUTION

LK, KM, DK, ÁV, LC, MP, FI, ÁA, MT and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. LK, KM, PH, ZsSz, KP and IM drafted the manuscript, GyL, SB,

AV, LB, MD and Asz edited the manuscript. ZsSz, KP, IT, ASz edited the figures and tables.

All authors read and approved the final manuscript.

During the study IT, ÁV, LC, MP and MT are going to manage the endoscopic treatments. LP, DK, GyL, ZssZ, MD and SB are responsible for cholecystectomies. ITAB and SC members are listed ahead.

LIST OF ABBREVATIONS

ABP – acute biliary pancreatitis

ASA – American Society of Anesthesiologists

CECT – contrast enhanced computed tomography

DCP – Data Cleaning Plan

DMP – Data Management Plan

ES – endoscopic shicterotomy

eCRF – electronic case report form

ESGE – European Society of Gastrointestinal Endoscopy

HPSG – Hungarian Pancreatic Study Group

IDMB – Independent Data Management Board

ITAB – International Translational Advisory Board

ITT – Intent to Treat

LC – Laparoscopic cholecystectomy

PPS – Per Protocol Set

SAS – Safety Analysis Set

SC – Steering Comittee

References

1. Peery AF, Dellon ES, Lund J, Crockett SD, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179–87. doi: 10.1053/j.gastro.2012.08.002

2. Dhiraj Y, Albert BL. The epidemiology of pancreatitis and pancreatic cancer gastroenterology. Gastroenterology 2013;144(6):1252–1261. doi: 10.1053/j.gastro.2013.01.068

3. Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. Schepers et al. Trials 2016;17:5. doi: 10.1186/s13063-015-1132-0

4. Uhl W, Müller CA, Krähenbühl L et al. Acute gallstone pancreatitis, Timing of laparoscopic cholecystectomy in mild and severe disease. SurgEndosc 1999;13:1070–1076

5. Schietroma M, Carlei F, Lezoche E, et al. Acute biliary pancreatitis: staging and management. Hepato-gastroenterology 2001;48(40):988–993

6. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–iii9. doi: 10.1136/gut.2004.057026

7. Forsmark CE, Baillie J. AGA institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–2044. doi: 10.1053/j.gastro.2007.03.065.

8. van Baal MC, Besselink MG, Bakker OJ, et al. for the Dutch Pancreatitis Study Group: Interval cholecystectomy after mild biliary pancreatitis is associated with a high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. Annals of Surgery 2012;255(5):860–866. doi: 10.1097/sla.0b013e3182507646

9. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400. doi: 10.1111/j.1572-0241.2006.00856.x.

10. Uhl W, Warshaw A, Imrie C, et al. IAP Guidelines for the Surgical Management of Acute Pancreatitis. Pancreatology 2002;2:565–573. doi: 10.1159/000067684

11. Nealon WH, Bawduniak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. Ann Surg 2004;239:741–749. doi:10.1097/01.sla.0000128688.97556.94

12. da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicenter randomized controlled trial. Lancet 2015;386:1261–68. doi: 10.1016/s0140-6736(15)00274-3

13. Paul GL, Bettina WD, Markus ML. Clinical perspectives in pancreatology: Compliance with Acute Pancreatitis Guidelines in Germany. Pancreatology 2005;5:591–593. doi: 10.1159/000087501

14. Uomo G, Manes G, Laccetti M, et al. Endoscopic sphincterotomy and recurrence of acute pancreatitis in gallstone patients considered unfit for surgery. Pancreas 1997;14:28–31.

15. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583

16. Hritz I, Hegyi P. Early Achievable Severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. J Gastrointestin Liver Dis 2015;24(2):177–82. doi: 10.15403/jgld.2014.1121.242.easy

17. Párniczky A, Mosztbacher D, Zsoldos F et al. Analysis of Pediatric Pancreatitis (APPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):105–10. doi: 10.1159/000441353

18. Zsoldos F, Párniczky A, Mosztbacher D, et al. Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):121–6. doi: 10.1159/000441352

19. Dubravcsik Z, , Madácsy L, Gyökeres T, et al. Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology 2015;15(2):115–23. doi: 10.1016/j.pan.2015.02.007

20. Márta K, Szabó AN, Pécsi D, et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open 2017;7(9):e015874. doi: 10.1136/bmjopen-2017-015874

21. Dubravcsik Z, Farkas G, Hegyi P, et al. [Autoimmune pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):292–307. doi: 10.1556/OH.2015.30061

22. Hritz I, Czakó L, Dubravcsik Z, et al. [Acute pancreatitis. Evidence-based practice guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):244–61. doi: 10.1556/OH.2015.30059

23. Parniczky A, Czakó L, Dubravcsik Zs, et al. [Pediatric pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):308–25. doi: 10.1556/OH.2015.30062

24. Takacs T, Czakó L, Dubravcsik Z, et al. [Chronic pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):262–88. doi: 10.1556/OH.2015.30060

25. Bouwense SA, Besselink MG, van Brunschot S, et al. Pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial): study protocol for a randomized controlled trial. Published online 26 Nov 2012. doi: 10.1186/1745-6215-13-225

26. Pier AT, Alberto M, Lars A, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016 Jul;48(7):657-83. doi: 10.1055/s-0042-108641

27. Edmund AMN, Hans T, CK Kum, et al. EAES Clinical Practice Guidelines on Laparoscopic Cholecystectomy, Appendectomy, and Hernia Repair (1994). In: EAES guidelines for endoscopic surgery: Twelve years evidence-based surgery in Europe. E. Neugebauer, S. Sauerland, A.B. Fingerhut, B. Millat, G.F. Buess (Eds.). Springer Berlin Heildelberg, 2006:265-289

28. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20(45):16891. doi: 10.3748/wjg.v20.i45.16891

29. Banks PA, Bollen TL, Dervenis C, et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2012;62(1):102-11. doi: 10.1136/gutjnl-2012-302779

30. van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. Ann Surg 2009;250:68–75. doi: 10.1097/SLA.0b013e3181a77bb4

31. Keus F, de Jong JA, Gooszen HG, van Laarhoven CJ: Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database Syst Rev 2006;4:CD006231. doi: 10.1002/14651858.cd006231

32. Mayumi T, Takada T, Kawarada Y, et al. Results of the Tokyo Consensus Meeting Tokyo Guidelines. J Hepatobiliary Pancreat Surg 2007;14:114–121. doi: 10.1007/s00534-006-1163-8

33. Max JS, Douglas AD. What Is New in Rome IV. Journal of Neurogastroenterology and Motility 2017; 23(2): 151-163. doi: 10.5056/jnm16214

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline (34).

** no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1)diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST*

*** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old*

Figure 2 Shows the evaluation of primary and secondary endpoints.

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15]

**In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct.*

***These criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for opioid analgesics; (3) declining C-reactive protein levels and <100 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) resumed oral intake on the part of the patient; and (6) ERCP/ES without complications.* Befor discharge or transfer to surgery department.

**** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after cholecystectomy to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q=question)*

Figure 4 The listed parameters were used to estimate results for the current sample size.

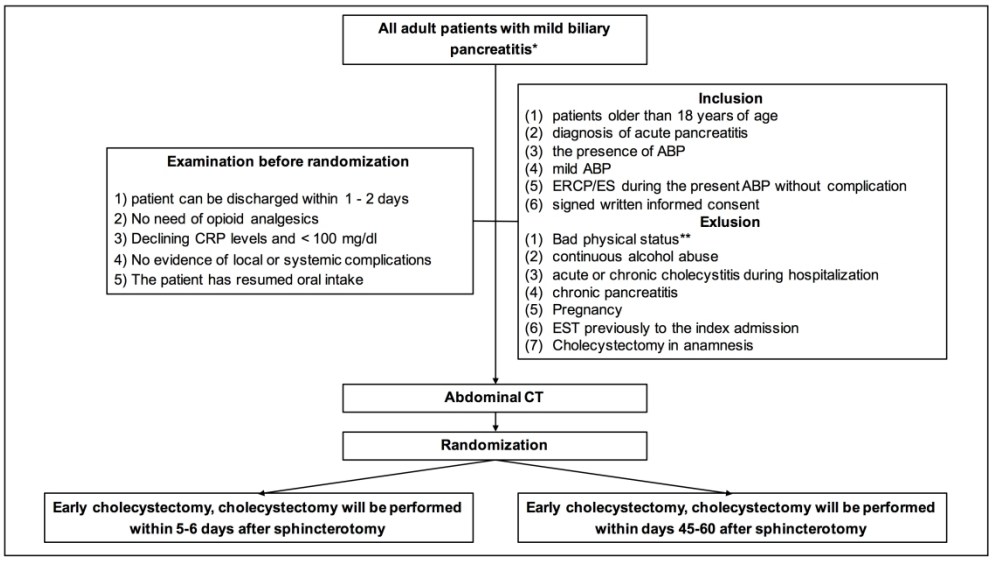

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline (34).
* no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1)diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST
** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old

265x151mm (300 x 300 DPI)

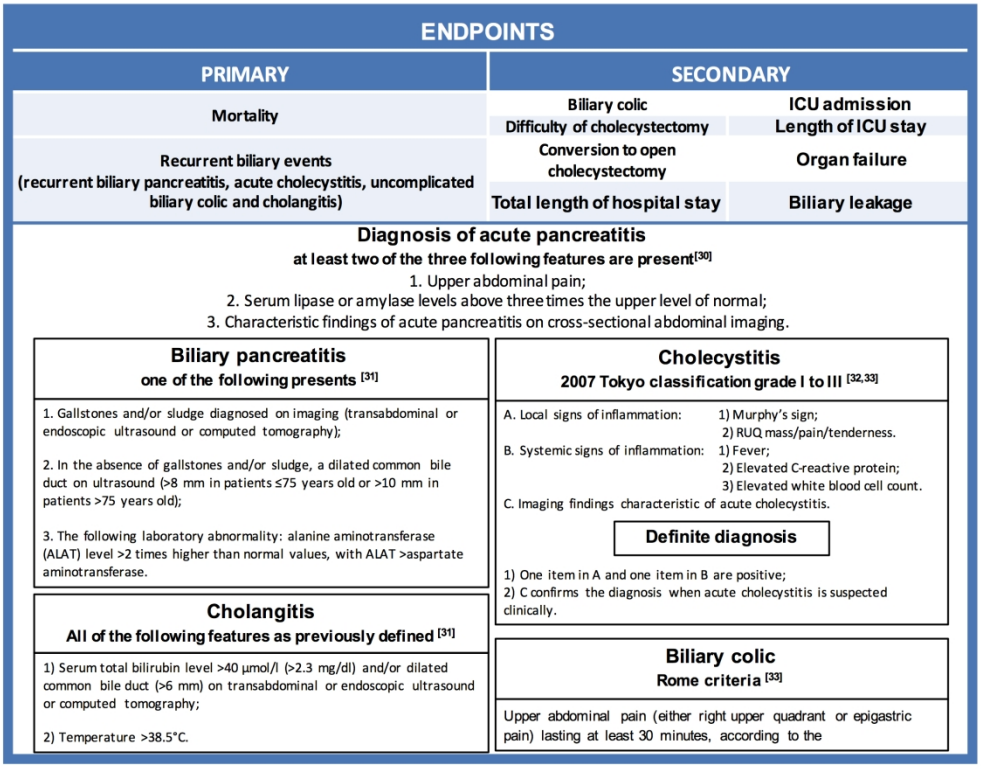

Figure 2 Shows the evaluation of primary and secondary endpoints.

198x154mm (300 x 300 DPI)

STUDY PERIOD							
DIVISION	Gastroenterology management				Department of Surgery		Control visit
SERVING	DOCTOR no.1 and no.2				DOCTOR no.3		DOCTOR no.4
	1	1	2	1			
OBJECT	MBP management and randomization				Cholecystectomy after ES		Follow up
TIMEPOINT	– several days	0		+ several days	Within 5-6 days	Between day 45-60	Day 90±7 after ES
ENROLMENT:							
Diagnosis of acute biliary pancreatitis*	X						
Endoscopic sphincterotomy		X					
Eligibility screen			X Q2-4				
TEST 1**				X Q5			
Sign of Informed consent form				X Q6			
Allocation***				X Q6			
Randomization***				X Q6			
Discharge**** to home or to surg.				X			
INTERVENTIONS:							
Group A Early cholecystectomy					X		
Group B Delayed cholecystectomy						X	
TEST 2**					X Q7	X Q7	
ASSESSMENTS:							
Follow up (with the help of an							X

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15]

*In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct.

**These criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for opioid analgesics; (3) declining C-reactive protein levels and <100 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) resumed oral intake on the part of the patient; and (6) ERCP/ES without complications. Befor discharge or transfer to surgery department.

*** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after cholecystectomy to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q=question)

269x154mm (300 x 300 DPI)

Hypothesised proportion in each group	Significance level	Power	Acceptable max. difference for equivalency	Sample size needed for analysis (per group)	Sample size for screening (with 5% drop-out rate)
5%	95%	90%	14%	42	89

Figure 4 The listed parameters were used to estimate results for the current sample size.

271x39mm (300 x 300 DPI)

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROU

QUESTIONNAIRE

1. Personal data

1.1 Patient's data

Name:_____ Sex: Male / Female

Date of Birth:_____ Age:_____

Insurance number:_____

Phone number:_____ The patient's study number:

1.2 Doctors' data

DOCTOR No. 1:

Name of the doctor **responsible for the treatment of ABP**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 2:

Name of the doctor **responsible for the randomization**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 3:

Name of the doctor **responsible for the operation**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 4:

Name of the doctor **responsible for the 90 days' visit**: _____

The phone number of the doctor:_____

Institute: _____

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROU

2. Inclusion criteria /DOCTOR No. 2/

Patients older than 18 age	**YES**	**NO**
Diagnosis of acute pancreatitis (two of them have to be positive) - upper abdominal pain - serum lipase or amylase is three times higher of upper limit of normal - characteristic findings of acute pancreatitis on abdominal imaging	**YES**	**NO**
Presence of biliary pancreatitis (one of them has to be true) - diagnosis of gallstone or sludge on imaging - the absence of gallstone or sludge with a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years of age or >10 mm in patients >75 years old) - alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Mild acute biliary pancreatitis (all of them have to be true) /HAS TO BE DETERMINED AT DISCHARGE OF THE PATIENT/ - no peripancreatic fluid collections - no pancreatic necrosis - no transient or persistent organ failure	**YES**	**NO**
ERCP/ES without complications	**YES**	**NO**
Written informed consent	**YES**	**NO**
One „NO" is present = DO NOT INCLUDE!		

3. Exclusion criteria /DOCTOR No. 2/

American Society of Anesthesiologists (ASA) classification - III patients >75 years old - IV, V, VI. Groups	**YES**	**NO**
Acute or chronic cholecystitis during hospitalization	**YES**	**NO**
Previous sphincterotomy or cholecystectomy	**YES**	**NO**
Continuous alcohol abuse or chronic pancreatitis	**YES**	**NO**
Pregnancy	**YES**	**NO**
One „YES" is present = EXCLUDE!		

4. If all inclusions and no exclusion criteria are met, than the physician may indicate the patient to participate in the study. / DOCTOR No. 2/

The treating physician (DOCTOR No. 2) anticipates that the patient can be discharged	**YES**	**NO**
No need for ~~opioid~~ analgesics	**YES**	**NO**
Declining C-reactive protein levels and <100 mg/l	**YES**	**NO**
No evidence of local or systemic complications	**YES**	**NO**
The patient has resumed solid oral nutrient	**YES**	**NO**
If all YES = RANDOMIZATION /see point 6/		

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROU

5. Medical History and characteristics of ABP / DOCTOR No. 1/

Date of admission (diagnosis of AP):……

Date of discharge: ……

5.1 Anamnesis

History of upper abdominal surgery: Yes / No
If yes, interventions:……
……
History if biliary colics Yes / No
History of cholecystitis Yes / No
Fever Yes / No .....°C
Diabetes Yes / No
Antibiotic therapy during the ABP Yes / No

BMI Weight:____ kg, Height:____ cm, BMI:____ kg/m^2

ASA classification (ASA PHYSICAL STATUS CLASSIFICATION SYSTEM)

I. group(**Normal** healthy patient)	**YES**	**NO**
II. group(Patient with **mild systemic disease** with no functional limitations)	**YES**	**NO**
III. group(Patient with **moderate** systemic disease **with functional limitations**)	**YES**	**NO**

5.2. Laboratory measurements

At discharge after AP:

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alkaline phosphatase(U/l)	

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROU

5.3. Pancreatic imaging /At discharge after AP/

5.3.1 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

Please NOTE! Abdominal CT is compulsory when the patient is discharged

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:** ☐
- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …….. cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter: …….. mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……
  - none

Other Description:
……
……
……
……

5.4. Characteristics of AP

Date of diagnosis (admission)……..……

Date of EST: ……

Date of discharge: ……

Endoscopic sphincteroto**M**y for delay**I**ng cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

6. Randomization / DOCTOR No. 2/

The patient will be randomized by an internet randomization module in the following 2 groups:

Randomization:

A. Early cholecystectomy (within 6 days after ERCP/ES)

B. Delayed cholecystectomy (between 45 and 60 days after ERCP/ES)

Please circle the relevant group after randomization: A or B

Please inform the patient concerning the **1)** Date for imaging examination and blood measurements before the operation, **2)** Date for the operation, **3)** Date for the 90 days visit

7. Operation /responsibility of DOCTOR No. 3/

Date of operation: ……

Length of days between ES and operation: ……

If the operation is not in the time period described in point 6 please provide the reason: ……

7.1 Anamnesis (between discharge after ABP and operation)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis** 1) One item in A and one item in B are positive; 2) C confirms the diagnosis when acute cholecystitis is suspected clinically	**YES**	**NO**
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers is **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reasons for hospitalization: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

7.2 Laboratory measurements (no more than 24h before the operation)

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alcaline phosphatase(U/l)	

If the patient is in group A, and the operation is performed within 24h after the blood samples are taken during the discharge of the patients, NO ADDITIONAL BLOOD SAMPLE HAS TO BE TAKEN. Please copy the values from 5.2.

7.3 Pancreatic imaging

7.3.1 Abdominal ultrasonography:

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size: …… cm

- **Wirsung** dilatation: YES / NO (yes, diameter: …….. mm)

Other Description:
……
……
……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROU

7.3.2 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:** ☐
- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**: …… cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: …… cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area: …… cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter: …… mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter: …… cm)
  - Both sides, L - …… cm, R - …… cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: ……
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: ……
  - none

Other Description:
……
……
……
……

If the patient is in group A, and the operation is performed within 24h after the imaging is performed during the discharge of the patients, NO ADDITIONAL IMAGING EXAMINATION HAS TO BE ORDERED. Please copy the details from 5.3.

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

HUNGARIAN PANCREATIC STUDY GROU

7.4. Characteristics of the Operation

The dificulty of cholecystectomy(10 – hard, 5 – average difficulty):

1	2	3	4	5	6	7	8	9	10

Conversion to open cholecystectomy: Yes / No
The lenght of the operation (min):_____
Days spent in hospital after cholecystectomy:_____
Intenziv unit care: Yes / No
Mortality: Yes / No
Haemorrhage, reintervention needed: Yes / No
No Iatrogenic perforation of the gallbladder Yes / No
Common bile duct (CBD) injuries Yes / No
Bile leakage Yes / No
Sub-hepatic abscess Yes / No

8. Visit 90 days after ES / DOCTOR No. 4/

The visit has to be completed +/- 7 days (between 83 and 97 days after ES)

Date of the visit: ……

Length of days between ES and visit: ……

8.1 Anamnesis (between the operation and visit)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis**	**YES**	**NO**

Endoscopic sphincteroto**M**y for delay**I**ng
Long-term **A**nd one**L**ine **V**ia **P**ancreatitis

1) One item in A and one item in B is positive; 2) C confirms the diagnosis when acute cholecystitis is suspected clinically		
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reason for hospitalization: ……

SIGNATURES:

Doctor No.1…….. **Date:……..**

Doctor No.2…….. **Date:……..**

Doctor No.3…….. **Date:……..**

Doctor No.4…….. **Date:……..**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	3	Date and version identifier	8
Funding	4	Sources and types of financial, material, and other support	8
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 9
	5b	Name and contact information for the trial sponsor	3, 8
	5c	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	4
	5d	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)	3, 4, 6-7

Introduction			
Background and rationale	6a	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	3
	6b	Explanation for choice of comparators	3, 8
Objectives	7	Specific objectives or hypotheses	4, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	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	4, 7-8,
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	12	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	6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	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	5
Allocation concealment mechanism	16b	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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis			
Data collection methods	18a	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	6

	18b	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	6
Data management	19	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	7
Statistical methods	20a	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	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	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	7
	21b	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	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3, 8
Protocol amendments	25	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)	6
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	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	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy	31a	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	8

	31b	Authorship eligibility guidelines and any intended use of professional writers	8
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	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	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025551.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2019
Complete List of Authors:	Kucserik, Levente; Universitatea de Medicina si Farmacie din Targu Mures, Division of Surgery Márta, Katalin; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine; János Szentágothai Research Center, University of Pécs Vincze, Áron; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Division of Gastroenterology, First Department of Internal Medicine; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine Lázár, György; University of Szeged, Department of Surgery Czakó, László; University of Szeged, First Department of Medicine Szentkereszty, Zsolt; University of Debrecen, Department for Surgery Papp, Maria; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Palatka, Károly; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Izbéki, Ferenc; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Divison of Gastroenterology Altorjay, Áron; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Division of Surgery Török, Imola; Universitatea de Medicina si Farmacie din Targu Mures, Division of Gastroenterology Barbu, Sorin; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Tantau, Marcel; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Vereczkei, András; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department for Surgery Bogár, Lajos; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department of Anaesthesiology and Intensive Therapy Dénes, Márton; County Hospital Targu Mures Németh, Imola; Adware Research Developing and Consulting Ltd Szentesi, Andrea; Pecsi Tudomanyegyetem, Institute for Translational Medicine; Szegedi Tudomanyegyetem, MTA-SZTE Translational Gastroenterology Research Group Zádori, Noémi; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine Antal, Judit; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine

	Lerch, Markus; Universitatsmedizin Greifswald, Department of Medicine A Neoptolemos, John; University of Liverpool Department of Molecular and Clinical Cancer Medicine Sahin-Toth, Miklos; Boston University Petersen, Ole; Cardiff University, Medical Research Council Group Kelemen, Dezső; Pecsi Tudomanyegyetem, Surgery Clinic Hegyi, Péter; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine; MTA-SZTE Translational Gastroenterology Research Group
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Levente-Pál Kucserik MD[1], Katalin Márta MD[2,3], Áron Vincze MD PhD[2,4], György Lázár MD PhD DSc[5], László Czakó MD PhD DSc[6], Zsolt Szentkereszty MD PhD[7], Mária Papp MD PhD[8], Károly Palatka MD PhD[8], Ferenc Izbéki MD PhD DSc[9], Áron Altorjay MD PhD DSc[10], Imola Török MD[11], Sorin Barbu MD PhD[12], Marcel Tantau MD PhD[12], András Vereczkei MD PhD DSc[13], Lajos Bogár MD PhD DSc[14], Márton Dénes MD[15], Imola Németh PhD[16], Andrea Szentesi PhD[2,21], Noémi Zádori MD[2], Judit Antal PhD[2], Markus M. Lerch MD PhD DSc[17], John Neoptolemos MD PhD DSc[18], Miklos Sahin-Tóth MD PhD DSc[19], Ole H. Petersen MD PhD DSc[20], Dezső Kelemen* MD PhD[13], Péter Hegyi* MD PhD DSc[2,21].

1 Division of Surgery, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
2 Insitute for Translational Medicine, University of Pécs Medical School, Pécs, HU
3 János Szentágothai Research Center, University of Pécs, Pécs, HU
4 Division of Gastroenterology,First Department of Internal Medicine, University of Pécs Medical School, Pécs, HU
5 Department of Surgery, University of Szeged, Szeged, HU
6 First Department of Medicine, University of Szeged, Szeged, HU
7 Department for Surgery, University of Debrecen, Debrecen, HU
8 Division of Gastroenterology, University of Debrecen, Debrecen, HU
9 Divison of Gastroenterology, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehérvár, HU
10 Divison of Surgery, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehérvár, HU
11 Division of Gastroenterology, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
12 4th Department of Surgery, University of Medicine & Pharmacy "Iuliu Hatieganu" Cluj, RO
13 Surgery Clinic, University of Pécs, Pécs, HU
14 Department of Anaesthesiology and Intensive Therapy, University of Pécs Medical School, Pécs, HU
15 County Hospital Targu Mures, Targu Mures, RO
16 Adware Research Developing and Consulting Ltd., Balatonfüred, HU
17 Department of Medicine A, University Medicine Greifswald, Germany
18 Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK
19 Center for Exocrine Disorders, Department of Molecular and Cell Biology, Boston, USA; University Henry M. Goldman School of Dental Medicine, Boston, Massachusetts, USA
20 Medical Research Council Group, Cardiff School of Biosciences, Cardiff University, Cardiff, CF10 3AX, Wales, UK
21 Hungarian Academy of Sciences - University of Szeged, Translational Multidisciplinary Research Group, Szeged, Hungary

*: equally contributed

E-mail addresses of the authors:

LPK k.levente.p@gmail.com, KM katalin.marta@aok.pte.hu, ÁV vincze.aron@pte.hu, GyL lazar.gyorgy@med.u-szeged.hu, LC czako.laszlo@med.u-szeged.hu,, ZsSz szentkerzs@freemail.hu, MP papp.maria@med.unideb.hu, KP palatka@med.unideb.hu, FI fizbeki@gmail.com, ÁA altorjay@mail.fmkorhaz.hu, IT torokimola@gmail.com, SB barbu@pancreasclub.ro, MT matantau@gmail.com, AV vereczkei.andras@pte.hu, , LB bogar.lajos@pte.hu, MD denesmatyi@yahoo.com, , IN imola.nemeth@adwareresearch.com,, ASz szentesiai@gmail.com, NZ znoeemi@gmail.com, JA juditantal2014@gmail.com, MML lerch@uni-greifswald.de, JN jneoptolemos1@gmail.com, MST miklos@bu.edu, OHP PetersenOH@cardiff.ac.uk, DK kelemende@gmail.com, PH p.hegyi@tm-centre.org

Corresponding Investigator: Péter Hegyi MD, PhD, DSc

Phone: +(36-70) 375-1031

e-mail: p.hegyi@tm-centre.org

Coordinating institution: University of Pecs – Medical School

Institute for Translational Medicine

12 Szigeti Street, PÉCS, H-7624, HUNGARY

FAX: +(36-72) 536-247

Phone: +(36-72) 536-246

web: www.tm-centre.org

ABSTRACT

Introduction. According to the literature, early cholecystectomy is necessary to avoid complications related to gallstones after an initial episode of acute biliary pancreatitis (ABP). A randomized, controlled multicenter trial (the PONCHO trial) revealed that in the case of gallstone-induced pancreatitis, early cholecystectomy was safe in patients with mild gallstone pancreatitis and reduced the risk of recurrent gallstone-related complications, as compared with interval cholecystectomy. We hypothesize that carrying out a sphincterotomy (ES) allows us to delay cholecystectomy, thus making it logistically easier to perform and potentially increasing the efficacy and safety of the procedure.

Methods/Design. EMILY is a prospective, randomized, controlled multicenter trial. The patients are randomized to two groups: (1) early cholecystectomy (within 6 days after discharge) and (2) patients with delayed (interval) cholecystectomy (between 45 and 60 days after discharge). During a 12-month period, 89 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (that is, recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The secondary endpoints are organ failure, biliary leakage, technical difficulty of the cholecystectomy, surgical and other complications.

Ethics and dissemanitaion. The trial has been registered at the ISRCTN (ref no. 10667869) and approved by the relevant organisation, the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Keywords: acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

Strengths and limitation

Strength 1: The study is designed as a prospective, randomized-controlled trial to achieve conclusion on the highest evidence level to provide the first evidence concerning the possible benefits of ES on timing cholecystectomy, it is (i) multinational (ii) multicentric, (iii) internationally registered and (iv) the pre-study protocol is published.

Strength 2: Only high volume, expert centers can join to the study. They have to provide (i) laparoscopically trained surgeons with >100 laparoscopic procedures performed and (ii) if ERCP/ES is provided during the index admission, trained gastroenterologist with >50 ES completed within a year must be on duty.

Strength 3: The study enjoys continuous support from (i) an International Translational Advisory Board (ITAB) including top, well-established experts from different are of research field (ii) an Independent Data Management Board (IDMB).

Strength 4: The final conclusion can be achieved with low number of patients within a relatively short period.

Limitation 1: The study will provide evidence in a selected population (mild ABP who underwent ERCP+ES) and no evidence concerning the usefulness of ES in moderate and severe ABP.

INTRODUCTION

Acute pancreatitis is one of the leading gastrointestinal causes of acute hospital admissions [1, 2]. In most cases, it is caused by gallstones, sludge or edema [3]. Gallstone-induced pancreatitis involves a pathophysiologic factor, namely a distal common channel of the biliary and pancreatic ducts, which can be found in 80% of acute biliary pancreatitis (ABP) [4]. Acute biliary pancreatitis is a clinical entity with high rates of morbidity (15–50%) and mortality (20–35%) [5]. After ABP, several complications may occur; recurrent acute pancreatitis, cholestasis and fistula affecting the hepatobiliary system or other biliary events, such as acute cholecystitis, obstruction of the common biliary duct, cholangitis or biliary colic [6, 7]. Interval cholecystectomy after mild ABP is associated with a high risk of readmission for recurrent biliary events, especially after recurrent ABP [8]. The international practice guidelines recommend that in case of cholangitis or choledocholthiasis an ERCP should be performed to clear the bile duct with endoscopic sphincterotomy (ES). In addition, cholecystectomy should also be performed to avoid complications related to recurrent biliary events [9, 10]. In patients with clinically severe pancreatitis, with local complications, such as pancreatic necrosis or organ failure, the intervention namely the laparoscopic cholecystectomy (LC) is delayed 6 months until complications are resolved [11]. In cases of mild ABP, cholecystectomy is recommended between days 7 and 21 [4]. The latest studies show that after discharge of patients with ABP, cholecystectomy could reduce the risk of a recurrent ABP and other gallstone-induced complications [12]. In this setting, surgeons still prefer delayed cholecystectomy for efficacy and safety and for logistical reasons [13]. Some publications draw attention to ERCP/ES, which could reduce mortality and the formation of severe biliary complications [3, 14]. The aim of the EMILY trial is to combine a surgical treatment and a gastroenterological procedure to investigate if ES with delayed cholecystectomy (within 45 to 60 days after discharge) compared with ES with early cholecystectomy (within 6 days after discharge) could reduce recurrent biliary events.

METHODS

Design: EMILY is a prospective, randomized-controlled, multicenter trial. The patients are randomized to two groups: (1) Patients who undergo early cholecystectomy (within 6 days after discharge) and (2) patients who undergo delayed (interval) cholecystectomy (between 45 and 60 days after discharge). During a 12-month period, 89 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic and cholangitis). The secondary endpoints are: organ failure, biliary leakage, technical difficulty of cholecystectomy, and surgical and other complications.

This study was structured following the SPIRIT 2013 [15] guideline defining standard protocol items for clinical trials and got the relevant ethical approval EKU/2018/12176-5 (Scientific and Research Ethical Committee, Medical Research Council, Hungary).

Trial organization, committees and boards: The coordinator and designer of the EMILY study is the Centre for Translational Medicine at the Universityof Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Pancreatic Study Group (HPSG-coordinating society, www.pancreas.hu). The HPSG was established in 2011 to stimulate research in pancreatic diseases.

Until now, it has launched three international observational clinical studies in 2014 [16, 17, 18] (EASY, APPLE and PINEAPPLE) and two interventional studies (PREPAST [19] – 2014 and GOULASH [20] – 2017) and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [21, 22, 23, 24].

The following committees and boards will be involved: Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist).

The members in Szeged (HU) will be: LC (gastroenterologist), GL (surgeon); Debrecen (HU): MP (gastroenterologist), KP (gastroenterologist), ZS (surgeon); Pécs (HU): ÁV (gastroenterologist), DK (surgeon); Székesfehérvár (HU): FI (gastroenterologist), ÁA (surgeon); Targu Mures (RO): IT (gastroenterologist), LPK (surgeon); Cluj Napoca (RO): BS (surgeon), TM (gastroenterologist). KM is a trial management specialist, whereas AS leads the multidisciplinary core facility which will assist the scientists to run the study successfully. The SC will make decisions concerning all relevant questions including drop outs during the study.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

The study was designed by the SC and ITAB. It was funded by the University of Pécs, Medical School. The sponsor was not involved in the design of the study, and will have no access to database or the randomization code.

The study also contains an independent physician and safety manager as required by the ethical regulation.

Study population: All patients with mild ABP will be informed of the possibility to take part in the EMILY trial. After the consent form is signed participants will be randomized to 2 groups if they meet all the inclusion and no exclusion criteria (*Figure 1*).

Inclusion criteria: The criteria for inclusion in the study: (1) patients older than 18 years of age; (2) diagnosis of acute pancreatitis (at least 2 of the following 3 symptoms: upper abdominal pain, serum lipase or amylase is three times higher than the upper limit of normal and characteristic findings for acute pancreatitis on imaging); (3) the presence of ABP (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST; (4) mild ABP (meaning no pancreatic necrosis, no transient or persistent organ failure (>48 hours) is present; (5) ERCP/ES either during the index admission or in the medical history without complication (6) signed written informed consent (all included patient will sign the consent which contains the information about the trial and procedures) *(Figure 1)*.

Exclusion criteria: A patient's bad physical status can be an exclusion criterion. American Society of Anesthesiologists (ASA) III patients >75 years old; ASA IV or V patients, will be excluded. Patients with continuous alcohol abuse, acute or chronic cholecystitis during hospitalization, chronic pancreatitis, pregnancy, previous cholecystectomy will also be excluded *(Figure 1)*.

Time of randomization: 5 criteria are described by the PONCHO trial [25]. If these 5 criteria are met, the informed consent will be signed by the patient and a control abdominal CT will be carried out before discharge. These criteria are the following: (1) anticipation on the part of the treating physician that the patient can be discharged; (2) the patient has no abdominal pain and there is no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs. The patient must be randomized on the day of the discharge.

Randomization: The method of randomization is the following: The patient can be randomized by the study coordinator using a randomization module with sealed envelope. Patient data will be uploaded with the help of the administrator to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy *(Figure 1)*.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

Blinding: In prevention of patient's selection to group A and B trial participants, care providers and outcome assessors will be blinded until the allocation, as no access to randomization sequence. From assignment to intervention blinding cannot be provided considering the study characteristics (exact date of cholecystectomy). The allocation sequence is unblinded only to data analysts who are completely independent form medical team (decision making) and data collection.

Endpoints

Primary endpoint. The primary endpoint is a composite endpoint, which is based on mortality and on recurrent biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The observation period is three months. We decide based on criteria in *Figure 2* if a complication is present or not.

Secondary endpoints. We hypothesize that cholecystectomy for ABP between days 45-60 after discharge in patients with ES is as effective and safe as early cholecystectomy (within 6 day after discharge). In order to evaluate this, we will observe the following parameters: the number of biliary colic registered for the patient, difficulty of cholecystectomy (on a scale of 0-10, 0=easy, 5=moderately difficult, 10=hard, rate of conversion to open cholecystectomy, total length of hospital stay, need for ICU admission and total length of ICU stay, organ failure and biliary leakage *(Figure 2)*.

Treatment protocol

Randomization: Group A. Early cholecystectomy

Group B. Delayed cholecystectomy

We randomize patients into two groups after discharge *(Figure 3):*

Group A: The patient is randomized to the early cholecystectomy group, and cholecystectomy will be performed within 6 days after discharge.

Group B: The patient is randomized to the delayed cholecystectomy group, and the cholecystectomy will be carried out between 45 to 60 days.

Discontinuing or the modification of the allocated interventions for a trial participant is based on surgical causes like contraindicated opus, need for convertion to open cholecystectomy, or when the patient does not present to the hospital for cholecystectomy. Switching over the two interventions is not possible considering the trial characteristics, however in case of acute cholecystitis acute cholecystectomia can be performed independently from this trial. The case must be presented to SC.

Surgical details and quality control: If it will be the first ERCP/ES performed in the patient's medical history it will be performed according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines. [26] The laparoscopic cholecystectomy will follow the European Association Guidelines for Endoscopic Surgery [27]. The patients will be operated on by laparoscopically trained surgeons with >100 laparoscopic procedures performed and by a trained gastroenterologist with >50 ES completed within a year must be on duty if ERCP/ES is provided during the index admission. Centers which intend to randomize at least 15 patients and are able to perform an early cholecystectomy and ERCP/ES are eligible to participate in the study. In those centers which ES data will then be collected on the incidence of choledocholithiasis, percentage bile duct injury, duration, and perceived difficulty (on a scale of 0-10).

Diagnosing and treating ABP: In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ERCP should be performed only in the case of cholangitis or choledocholthiasis, to clear the bile duct with endoscopic sphincterotomy (ES) as described in the IAP/APA guideline. When only the laboratory parameters suggest common bile duct obstruction or choledocholthiasis, MRCP/EUS should be carried out [10].

Data collection and follow-up: Data will be collected in a personalized database, and follow-up will consist of questionnaires *(Supplementary File)*. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator.

The personal information about enrolled participants will only be shared with IDMB as uploaded data for randomization, after data analysis only randomization code will be used for identification to protect confidentiality during, and after the trial. Only the principal investigator and the IDMB will have access to the final trial dataset. However only identification code is used, we can aside from duplicated patient's data as cholecystectomy can not be performed twice.

Sample size estimation method

Primary endpoint: a composite of gallstone-related complications or mortality occurring within 6 months after discharge.

Hypothesis: With regard to our hypothesis, based on a non-inferiority design, there is no difference between the two groups (5%) in mortality or readmission for gallstone-related complications within 3 months after discharge.

Starting point: Sample size estimation was based on the results obtained by the PONCHO trial carried out on 264 patients, where a non-significant difference of 14% was obtained between the two study groups (3% in the same-admission cholecystectomy group compared to 17% in the interval admission group). Thus, using the hypothesized 5% for the occurrence of the primary endpoint in the same-admission cholecystectomy group and a max difference of 14% given by the results of the PONCHO trial a total sample size of 89 was obtained using a 5% drop-out rate. The sample size estimation results are listed in the table below *(Figure 4)*.

Data management and statistical analyses: Data will be handled by an independent Clinical Research Organizer. Electronic CRF (eCRF) will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager according to a Data Cleaning Plan (DCP). Adverse events will be coded using MedDRA according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements.

Safety Analysis Set (SAS, all patients enrolled in the study), Per Protocol Set (PPS, all enrolled patients who finished the study conforming to the requirements of the study protocol) and Intention to Treat (ITT, all randomized participants who start on a treatment, excluding consent withdrawals) will be performed.

Baseline patient and disease characteristics will be analyzed using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Descriptive statistics for both the primary and secondary parameters will be analyzed similarly.

Subgroup analyses will be perform concerning the imaging alterations (1: no gallstones or sludge on imaging, 2) sludge or 3) gallstone).

In case of important protocol modifications IDMB will report to the SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm

Premature termination of the study: In the interests of patient safety, an interim analysis will be conducted after 15 patients and after half of the presumed number of patients (45) have completed the study. IDMB will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subjects' right, safety and well-being and to guarantee the plausibility of clinical data. Similarity of groups at baseline will be also checked. The study will also be stopped if the two groups' results differ significantly ($p<0.001$). The study will be discontinued if the difference between the planned number of patients and the actual number is higher than 60% within one year. IDMB will report to SC.

Centers: The trial will be launched in four Hungarian (Szeged, Debrecen, Pécs and Székesfehérvár) and two Romanian centres (Targu Mures and Cluj Napoca), after which the study will be open to other centres. In all cases, the IDMB will conduct an audit of the center and will report to the SC. The SC maintains the right to decide whether a center meets the required quality to join the study.

The full protocol will we available for public in an open access journal.

Publication policy: We would like to publish the results in one of the internationally highly recognized decent journals**.** Centers providing more than 25 patients can provide 4 authors to the authorship list: 2 surgeons and 2 gastroenterologists.

Patient and Public Involvement: This pre-study protocol contains no results and data, therefore patients and or public were not involved.

DISCUSSION

In the case of early laparoscopic cholecystectomy, while dissection and logistics are more difficult [6, 7] compared with delayed (interval) cholecystectomy, it is still more effective. Delayed cholecystectomy in a mild form of ABP is preferred by many surgeons, but a number of complications can occur: recurrent ABP, acute cholecystitis, obstruction of ductus choledochus, and uncomplicated biliary colic [6, 7]. After ERCP/ES is performed, the common bile duct is cleared, the complications caused by gallstones or sludge are significantly reduced [28]. The EMILY study is designed to determine if ERCP/ES for mild ABP aids in delaying the cholecystectomy to day 45-60 after discharge among patients with ABP.

If an ES aids in delaying a cholecystectomy, then we can reduce early cholecystectomy-related complications and the surgeons can proceed with a safer, easier cholecystectomy using this method of treatment.

ACKNOWLEDGEMENTS

Funding: Center costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation. Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs-Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patient's life with research activities like registries, observational and interventional trial organizations (https://tm-centre.org).

There are no financial and other competing interests for principal investigators (LPK, DK), included patients or any member of the trial.

AUTHORS' CONTRIBUTION

LPK, KM, DK, ÁV, LC, MP, FI, ÁA, MT and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. LPK, KM, PH, ZsSz, KP drafted the manuscript, GyL, SB, AV, LB, MD, NZ, JA and ASz edited the manuscript. IN carried out the sample size calculation. ZsSz, KP, IT, NZ, JA, ASz edited the figures and tables. All authors read and approved the final manuscript.

During the study IT, ÁV, LC, MP and MT are going to manage the endoscopic treatments. DK, GyL, ZsSz, MD and SB are responsible for cholecystectomies. ITAB and SC members are listed ahead.

ETHICS AND DISSEMINATION

Trial registration: The trial has been registered at the ISRCTN10667869.

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Protocol Version: V1.0 10.07.2018.

Start of the patient recruitment: 1st March 2019

Additional information and future plan: Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will give informed consent. The samples will be stored at -80°C.

The post-trial care will follow the routine tratment protocols. In case if patient suffer a harm during hospitalization all of the responsability is taken by the hospital where the patient is treated.

LIST OF ABBREVATIONS

ABP – acute biliary pancreatitis

ASA – American Society of Anesthesiologists

CECT – contrast enhanced computed tomography

DCP – Data Cleaning Plan

DMP – Data Management Plan

ES – endoscopic shicterotomy

eCRF – electronic case report form

ESGE – European Society of Gastrointestinal Endoscopy

HPSG – Hungarian Pancreatic Study Group

IDMB – Independent Data Management Board

ITAB – International Translational Advisory Board

ITT – Intent to Treat

LC – Laparoscopic cholecystectomy

PPS – Per Protocol Set

SAS – Safety Analysis Set

SC – Steering Comittee

References

1. Peery AF, Dellon ES, Lund J, Crockett SD, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179–87. doi: 10.1053/j.gastro.2012.08.002

2. Dhiraj Y, Albert BL. The epidemiology of pancreatitis and pancreatic cancer gastroenterology. Gastroenterology 2013;144(6):1252–1261. doi: 10.1053/j.gastro.2013.01.068

3. Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. Schepers et al. Trials 2016;17:5. doi: 10.1186/s13063-015-1132-0

4. Uhl W, Müller CA, Krähenbühl L et al. Acute gallstone pancreatitis, Timing of laparoscopic cholecystectomy in mild and severe disease. SurgEndosc 1999;13:1070–1076

5. Schietroma M, Carlei F, Lezoche E, et al. Acute biliary pancreatitis: staging and management. Hepato-gastroenterology 2001;48(40):988–993

6. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–iii9. doi: 10.1136/gut.2004.057026

7. Forsmark CE, Baillie J. AGA institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–2044. doi: 10.1053/j.gastro.2007.03.065.

8. van Baal MC, Besselink MG, Bakker OJ, et al. for the Dutch Pancreatitis Study Group: Interval cholecystectomy after mild biliary pancreatitis is associated with a high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. Annals of Surgery 2012;255(5):860–866. doi: 10.1097/sla.0b013e3182507646

9. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400. doi: 10.1111/j.1572-0241.2006.00856.x.

10. Uhl W, Warshaw A, Imrie C, et al. IAP Guidelines for the Surgical Management of Acute Pancreatitis. Pancreatology 2002;2:565–573. doi: 10.1159/000067684

11. Nealon WH, Bawduniak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. Ann Surg 2004;239:741–749. doi:10.1097/01.sla.0000128688.97556.94

12. da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicenter randomized controlled trial. Lancet 2015;386:1261–68. doi: 10.1016/s0140-6736(15)00274-3

13. Paul GL, Bettina WD, Markus ML. Clinical perspectives in pancreatology: Compliance with Acute Pancreatitis Guidelines in Germany. Pancreatology 2005;5:591–593. doi: 10.1159/000087501

14. Uomo G, Manes G, Laccetti M, et al. Endoscopic sphincterotomy and recurrence of acute pancreatitis in gallstone patients considered unfit for surgery. Pancreas 1997;14:28–31.

15. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583

16. Hritz I, Hegyi P. Early Achievable Severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. J Gastrointestin Liver Dis 2015;24(2):177–82. doi: 10.15403/jgld.2014.1121.242.easy

17. Párniczky A, Mosztbacher D, Zsoldos F et al. Analysis of Pediatric Pancreatitis (APPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):105–10. doi: 10.1159/000441353

18. Zsoldos F, Párniczky A, Mosztbacher D, et al. Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):121–6. doi: 10.1159/000441352

19. Dubravcsik Z, , Madácsy L, Gyökeres T, et al. Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology 2015;15(2):115–23. doi: 10.1016/j.pan.2015.02.007

20. Márta K, Szabó AN, Pécsi D, et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open 2017;7(9):e015874. doi: 10.1136/bmjopen-2017-015874

21. Dubravcsik Z, Farkas G, Hegyi P, et al. [Autoimmune pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):292–307. doi: 10.1556/OH.2015.30061

22. Hritz I, Czakó L, Dubravcsik Z, et al. [Acute pancreatitis. Evidence-based practice guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):244–61. doi: 10.1556/OH.2015.30059

23. Parniczky A, Czakó L, Dubravcsik Zs, et al. [Pediatric pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):308–25. doi: 10.1556/OH.2015.30062

24. Takacs T, Czakó L, Dubravcsik Z, et al. [Chronic pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):262–88. doi: 10.1556/OH.2015.30060

25. Bouwense SA, Besselink MG, van Brunschot S, et al. Pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial): study protocol for a randomized controlled trial. Published online 26 Nov 2012. doi: 10.1186/1745-6215-13-225

26. Pier AT, Alberto M, Lars A, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016 Jul;48(7):657-83. doi: 10.1055/s-0042-108641

27. Edmund AMN, Hans T, CK Kum, et al. EAES Clinical Practice Guidelines on Laparoscopic Cholecystectomy, Appendectomy, and Hernia Repair (1994). In: EAES guidelines for endoscopic surgery: Twelve years evidence-based surgery in Europe. E. Neugebauer, S. Sauerland, A.B. Fingerhut, B. Millat, G.F. Buess (Eds.). Springer Berlin Heildelberg, 2006:265-289

28. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20(45):16891. doi: 10.3748/wjg.v20.i45.16891

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline [15]

** no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1) diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST*

*** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old*

Figure 2 Shows the evaluation of primary and secondary endpoints.

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15].

**Diagnosis of acute biliary pancreatitis (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST. In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ABP is mild, when there is no pancreatic necrosis, or no transient or persistent organ failure (>48 hours).*

***If it is necessary to perform endoscopic sphincterotomy during the current admission or ES in the medical history also acceptable.*

**** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q5, Q7, Q8, Q=question)*

***** The patient can be randomized by using a randomization module with sealed envelope. Patient data will be uploaded to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible*

to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

****** The criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs; and (6) ERCP/ES either during the index admission or in the medical history without complication. Before discharge or transfer to surgery department.*

Figure 4 The listed parameters were used to estimate results for the current sample size.

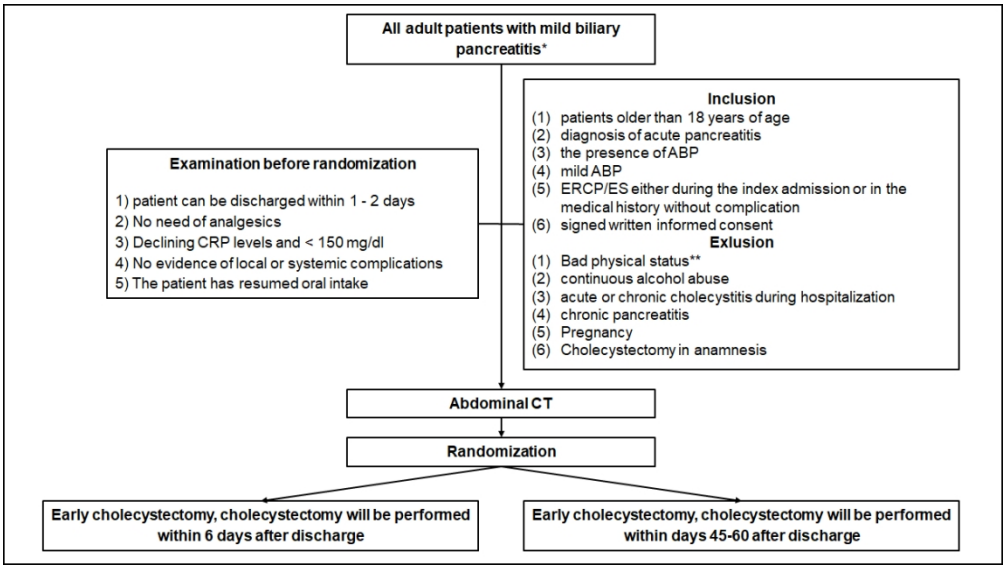

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline [15]
* no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1) diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST
** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old

105x59mm (300 x 300 DPI)

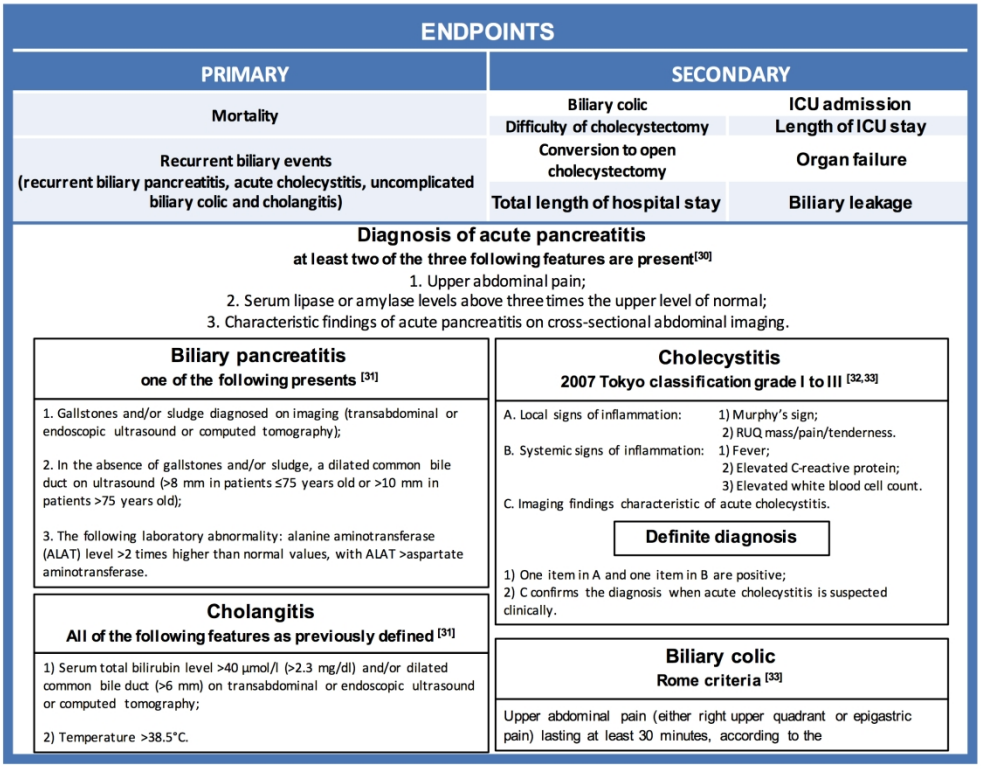

Figure 2 Shows the evaluation of primary and secondary endpoints.

198x154mm (300 x 300 DPI)

STUDY PERIOD							
DIVISION	Gastroenterology management				Department of Surgery		Control visit
SERVING	DOCTOR no.1 and no.2				DOCTOR no.3		DOCTOR no.4
	1	1	2	1			
OBJECT	MBP management and randomization				Cholecystectomy after discharge		Follow up
TIMEPOINT	– several days	0		+ several days	Within 6 days	Between day 45-60	Day 90±7 after discharge
ENROLMENT:							
Diagnosis of acute mild biliary pancreatitis*	X						
ES**		X					
Eligibility screen			X Q2-4				
TEST 1***				X Q5			
Sign of Informed consent form				X Q6			
Allocation****				X Q6			
Randomization****				X Q6			
Discharge***** to home or to surg.				X			
INTERVENTIONS:							
Group A Early cholecystectomy					X		
Group B Delayed cholecystectomy						X	
TEST 2***					X Q7	X Q7	
ASSESSMENTS:							
Follow up (with the help of an administrator***							X Q8

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15].

*Diagnosis of acute biliary pancreatitis (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST. In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ABP is mild, when there is no pancreatic necrosis, or no transient or persistent organ failure (>48 hours).

**If it is necessary to perform endoscopic sphincterotomy during the current admission or ES in the medical history also acceptable.

*** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q5, Q7, Q8, Q=question)

**** The patient can be randomized by using a randomization module with sealed envelope. Patient data will be uploaded to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

***** The criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs; and (6) ERCP/ES either during the index admission or in the medical history without complication. Before discharge or transfer to surgery department.

108x61mm (300 x 300 DPI)

Hypothesised proportion in each group	Significance level	Power	Acceptable max. difference for equivalency	Sample size needed for analysis (per group)	Sample size for screening (with 5% drop-out rate)
5%	95%	90%	14%	42	89

Figure 4 The listed parameters were used to estimate results for the current sample size.

271x39mm (300 x 300 DPI)

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY
HUNGARIAN PANCREATIC STUDY GROUP

QUESTIONNAIRE

1. Personal data

1.1 Patient's data

Name:_____ Sex: Male / Female

Date of Birth:_____Age:_____ Insurance number:__

_____

Phone number:_____ The patient's study number:

1.2 Doctors' data

DOCTOR No. 1:

Name of the doctor **responsible for the treatment of ABP**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 2:

Name of the doctor **responsible for the randomization**:_____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 3:

Name of the doctor **responsible for the operation**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 4:

Name of the doctor **responsible for the 90 days' visit**: _____

The phone number of the doctor:_____

Institute: _____

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

2. Inclusion criteria /DOCTOR No. 2/

Patients older than 18 age	**YES**	**NO**
Diagnosis of acute pancreatitis (two of them have to be positive) - upper abdominal pain - serum lipase or amylase is three times higher of upper limit of normal - characteristic findings of acute pancreatitis on abdominal imaging	**YES**	**NO**
Presence of biliary pancreatitis (one of them has to be true) - diagnosis of gallstone or sludge on imaging - the absence of gallstone or sludge with a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years of age or >10 mm in patients >75 years old) - alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Mild acute biliary pancreatitis (all of them have to be true) /HAS TO BE DETERMINED AT DISCHARGE OF THE PATIENT/ - no peripancreatic fluid collections - no pancreatic necrosis - no persistent organ failure	**YES**	**NO**
ERCP/ES either during the index admission or in the medical history without complication	**YES**	**NO**
Written informed consent	**YES**	**NO**
One „NO" is present = DO NOT INCLUDE!		

3. Exclusion criteria /DOCTOR No. 2/

American Society of Anesthesiologists (ASA) classification - III patients >75 years old - IV, V, VI. Groups	**YES**	**NO**
Acute or chronic cholecystitis during hospitalization	**YES**	**NO**
Previous cholecystectomy	**YES**	**NO**
Continuous alcohol abuse or chronic pancreatitis	**YES**	**NO**
Pregnancy	**YES**	**NO**
One „YES" is present = EXCLUDE!		

4. If all inclusions and no exclusion criteria are met, than the physician may indicate the patient to participate in the study. / DOCTOR No. 2/

The treating physician (DOCTOR No. 2) anticipates that the patient can be discharged	**YES**	**NO**
No need for analgesics	**YES**	**NO**
Declining C-reactive protein levels and <150 mg/l	**YES**	**NO**
No evidence of local or systemic complications	**YES**	**NO**
The patient has resumed solid oral nutrient	**YES**	**NO**
If all YES = RANDOMIZATION /see point 6/		

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

5. Medical History and characteristics of ABP / DOCTOR No. 1/

Date of admission (diagnosis of AP):……

Date of discharge: ……

5.1 Anamnesis

History of upper abdominal surgery: Yes / No
If yes, interventions:……
……
History if biliary colics Yes / No
History of cholecystitis Yes / No
Fever Yes / No .....°C
Diabetes Yes / No
Antibiotic therapy during the ABP Yes / No

BMI Weight:_____kg, Height:_____cm, BMI:_____kg/m^2

ASA classification (ASA PHYSICAL STATUS CLASSIFICATION SYSTEM)

I. group(**Normal** healthy patient)	**YES**	**NO**
II. group(Patient with **mild systemic disease** with no functional limitations)	**YES**	**NO**
III. group(Patient with **moderate** systemic disease **with functional limitations**)	**YES**	**NO**

5.2. Laboratory measurements

At discharge after AP:

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alkaline phosphatase(U/l)	

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

5.3. Pancreatic imaging /At discharge after AP/

5.3.1 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

Please NOTE! Abdominal CT is compulsory when the patient is discharged

- **CTSI:** ☐

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**.....cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area .....cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter .....cm)
  - Both sides, L - ……. cm, R .....cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: …….
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: …….
  - none

Other Description:
……
……
……
……

5.4. Characteristics of AP

Date of diagnosis (admission)……..……

Date of EST:…….

Date of discharge: ……

Endoscopic sphincteroto**M**y for delay**I**ng cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

6. Randomization / DOCTOR No. 2/

The patient will be randomized by an internet randomization module in the following 2 groups:

Randomization:

A. Early cholecystectomy (within 6 days after discharge)

B. Delayed cholecystectomy (between 45 and 60 days after discharge)

Please circle the relevant group after randomization:

A or B

Please inform the patient concerning the **1)** Date for imaging examination and blood measurements before the operation, **2)** Date for the operation, **3)** Date for the 90 days visit

7. Operation /responsibility of DOCTOR No. 3/

Date of operation: ……

Length of days between discharge and operation: ……

If the operation is not in the time period described in point 6 please provide the reason: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

HUNGARIAN PANCREATIC STUDY GROUP

7.1 Anamnesis (between discharge after ABP and operation)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis** 1) One item in A and one item in B are positive; 2) C confirms the diagnosis when acute cholecystitis is suspected clinically	**YES**	**NO**
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers is **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reasons for hospitalization: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.2 Laboratory measurements (no more than 24h before the operation)

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alcaline phosphatase(U/l)	

If the patient is in group A, and the operation is performed within 24h after the blood samples are taken during the discharge of the patients, NO ADDITIONAL BLOOD SAMPLE HAS TO BE TAKEN. Please copy the values from 5.2.

7.3 Pancreatic imaging

7.3.1 Abdominal ultrasonography:

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size.....cm

- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)

Other Description:
.....
.....
.....

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.3.2 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:** ☐
- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**.....cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area .....cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter .....cm)
  - Both sides, L - ……. cm, R .....cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: …….
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: …….
  - none

Other Description:
……
……
……
……

If the patient is in group A, and the operation is performed within 24h after the imaging is performed during the discharge of the patients, NO ADDITIONAL IMAGING EXAMINATION HAS TO BE ORDERED. Please copy the details from 5.3.

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.4. Characteristics of the Operation

The dificulty of cholecystectomy(10 – hard, 5 – average difficulty):

1	2	3	4	5	6	7	8	9	10

Conversion to open cholecystectomy: Yes / No
The lenght of the operation (min):_____
Days spent in hospital after cholecystectomy:_____
Intenziv unit care: Yes / No
Mortality: Yes / No
Haemorrhage, reintervention needed: Yes / No
No Iatrogenic perforation of the gallbladder Yes / No
Common bile duct (CBD) injuries Yes / No
Bile leakage Yes / No
Sub-hepatic abscess Yes / No

8. Visit 90 days after discharge / DOCTOR No. 4/

The visit has to be completed +/- 7 days (between 83 and 97 days after discharge)

Date of the visit: ……

Length of days between discharge and visit: ……

8.1 Anamnesis (between the operation and visit)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis**	**YES**	**NO**

Endoscopic sphincteroto**M**y for delay**I**ng
Long-term **A**nd **I**dem in **B**ile **Y**

1) cholecystectomy in mild acute biliary pancreatitis 2) C confirms the diagnosis when acute cholecystitis is suspected clinically		
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reason for hospitalization: ……

SIGNATURES:

Doctor No.1…….. Date:……..

Doctor No.2…….. Date:……..

Doctor No.3…….. Date:……..

Doctor No.4…….. Date:……..

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Description	Addressed on page number
Administrative information		
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	3
	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	Date and version identifier	10
Funding	Sources and types of financial, material, and other support	10
Roles and responsibilities	Names, affiliations, and roles of protocol contributors	1, 10
	Name and contact information for the trial sponsor	5, 10
	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	5
	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)	4,5, 8-9
Introduction		
Background and rationale	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	4
	Explanation for choice of comparators	4,8,9
Objectives	Specific objectives or hypotheses	5, 8
1		

Trial design	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes		
Study setting	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	5,8-9
Eligibility criteria	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7-8
	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	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	7
Participant timeline	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.3
Sample size	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	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	6

Allocation concealment mechanism	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	6
Implementation	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis		
Data collection methods	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	8
	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	8
Data management	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	8-9
Statistical methods	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	8
	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring		

Data monitoring	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	8-9
	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	9
Harms	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8-9
Auditing	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination		
Research ethics approval	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,10
Protocol amendments	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)	9
Consent or assent	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10-11
Confidentiality	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	8
Declaration of interests	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Access to data	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10-11
Dissemination policy	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	9
	Authorship eligibility guidelines and any intended use of professional writers	9
	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices		
Informed consent materials	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	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	10-11

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-025551.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Mar-2019
Complete List of Authors:	Kucserik, Levente; Universitatea de Medicina si Farmacie din Targu Mures, Division of Surgery Márta, Katalin; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine; János Szentágothai Research Center, University of Pécs Vincze, Áron; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Division of Gastroenterology, First Department of Internal Medicine; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine Lázár, György; University of Szeged, Department of Surgery Czakó, László; University of Szeged, First Department of Medicine Szentkereszty, Zsolt; University of Debrecen, Department for Surgery Papp, Maria; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Palatka, Károly; Debreceni Egyetem, Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Izbéki, Ferenc; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Divison of Gastroenterology Altorjay, Áron; Fejer County Saint George Teaching Hospital of Univerity of Pécs, Division of Surgery Török, Imola; Universitatea de Medicina si Farmacie din Targu Mures, Division of Gastroenterology Barbu, Sorin; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Tantau, Marcel; Universitatea de Medicina si Farmacie din Cluj Napoca, Division of Gastroenterology Vereczkei, András; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department for Surgery Bogár, Lajos; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Department of Anaesthesiology and Intensive Therapy Dénes, Márton; County Hospital Targu Mures Németh, Imola; Adware Research Developing and Consulting Ltd Szentesi, Andrea; Pecsi Tudomanyegyetem, Institute for Translational Medicine; Szegedi Tudomanyegyetem, MTA-SZTE Translational Gastroenterology Research Group Zádori, Noémi; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine Antal, Judit; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine

	Lerch, Markus; Universitatsmedizin Greifswald, Department of Medicine A Neoptolemos, John; University of Liverpool Department of Molecular and Clinical Cancer Medicine Sahin-Toth, Miklos; Boston University Petersen, Ole; Cardiff University, Medical Research Council Group Kelemen, Dezső; Pecsi Tudomanyegyetem, Surgery Clinic Hegyi, Péter; Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar, Institute for Translational Medicine; MTA-SZTE Translational Gastroenterology Research Group
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Surgery
Keywords:	acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial

Levente-Pál Kucserik MD[1], Katalin Márta MD[2,3], Áron Vincze MD PhD[2,4], György Lázár MD PhD DSc[5], László Czakó MD PhD DSc[6], Zsolt Szentkereszty MD PhD[7], Mária Papp MD PhD[8], Károly Palatka MD PhD[8], Ferenc Izbéki MD PhD DSc[9], Áron Altorjay MD PhD DSc[10], Imola Török MD[11], Sorin Barbu MD PhD[12], Marcel Tantau MD PhD[12], András Vereczkei MD PhD DSc[13], Lajos Bogár MD PhD DSc[14], Márton Dénes MD[15], Imola Németh PhD[16], Andrea Szentesi PhD[2,21], Noémi Zádori MD[2], Judit Antal PhD[2], Markus M. Lerch MD PhD DSc[17], John Neoptolemos MD PhD DSc[18], Miklos Sahin-Tóth MD PhD DSc[19], Ole H. Petersen MD PhD DSc[20], Dezső Kelemen* MD PhD[13], Péter Hegyi* MD PhD DSc[2,21].

1 Division of Surgery, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
2 Insitute for Translational Medicine, University of Pécs Medical School, Pécs, HU
3 János Szentágothai Research Center, University of Pécs, Pécs, HU
4 Division of Gastroenterology,First Department of Internal Medicine, University of Pécs Medical School, Pécs, HU
5 Department of Surgery, University of Szeged, Szeged, HU
6 First Department of Medicine, University of Szeged, Szeged, HU
7 Department for Surgery, University of Debrecen, Debrecen, HU
8 Division of Gastroenterology, University of Debrecen, Debrecen, HU
9 Divison of Gastroenterology, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehérvár, HU
10 Divison of Surgery, Fejer County Saint George Teaching Hospital of Univerity of Pécs, Székesfehérvár, HU
11 Division of Gastroenterology, Universitatea de Medicina si Farmacie din Targu Mures, Targu Mures, RO
12 4th Department of Surgery, University of Medicine & Pharmacy "Iuliu Hatieganu" Cluj, RO
13 Surgery Clinic, University of Pécs, Pécs, HU
14 Department of Anaesthesiology and Intensive Therapy, University of Pécs Medical School, Pécs, HU
15 County Hospital Targu Mures, Targu Mures, RO
16 Adware Research Developing and Consulting Ltd., Balatonfüred, HU
17 Department of Medicine A, University Medicine Greifswald, Germany
18 Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK
19 Center for Exocrine Disorders, Department of Molecular and Cell Biology, Boston, USA; University Henry M. Goldman School of Dental Medicine, Boston, Massachusetts, USA
20 Medical Research Council Group, Cardiff School of Biosciences, Cardiff University, Cardiff, CF10 3AX, Wales, UK
21 Hungarian Academy of Sciences - University of Szeged, Translational Multidisciplinary Research Group, Szeged, Hungary

*: equally contributed

E-mail addresses of the authors:

LPK k.levente.p@gmail.com, KM katalin.marta@aok.pte.hu, ÁV vincze.aron@pte.hu, GyL lazar.gyorgy@med.u-szeged.hu, LC czako.laszlo@med.u-szeged.hu,, ZsSz szentkerzs@freemail.hu, MP papp.maria@med.unideb.hu, KP palatka@med.unideb.hu, FI fizbeki@gmail.com, ÁA altorjay@mail.fmkorhaz.hu, IT torokimola@gmail.com, SB barbu@pancreasclub.ro, MT matantau@gmail.com, AV vereczkei.andras@pte.hu, , LB bogar.lajos@pte.hu, MD denesmatyi@yahoo.com, , IN imola.nemeth@adwareresearch.com,, ASz szentesiai@gmail.com, NZ znoeemi@gmail.com, JA juditantal2014@gmail.com, MML lerch@uni-greifswald.de, JN jneoptolemos1@gmail.com, MST miklos@bu.edu, OHP PetersenOH@cardiff.ac.uk, DK kelemende@gmail.com, PH p.hegyi@tm-centre.org

Corresponding Investigator: Péter Hegyi MD, PhD, DSc

Phone: +(36-70) 375-1031

e-mail: p.hegyi@tm-centre.org

Coordinating institution: University of Pecs – Medical School

Institute for Translational Medicine

12 Szigeti Street, PÉCS, H-7624, HUNGARY

FAX: +(36-72) 536-247

Phone: +(36-72) 536-246

web: www.tm-centre.org

ABSTRACT

Introduction. According to the literature, early cholecystectomy is necessary to avoid complications related to gallstones after an initial episode of acute biliary pancreatitis (ABP). A randomized, controlled multicenter trial (the PONCHO trial) revealed that in the case of gallstone-induced pancreatitis, early cholecystectomy was safe in patients with mild gallstone pancreatitis and reduced the risk of recurrent gallstone-related complications, as compared with interval cholecystectomy. We hypothesize that carrying out a sphincterotomy (ES) allows us to delay cholecystectomy, thus making it logistically easier to perform and potentially increasing the efficacy and safety of the procedure.

Methods/Design. EMILY is a prospective, randomized, controlled multicenter trial. All patients with mild ABP, who underwent ES during the index admission, or in the medical history will be informed to take part in EMILY study. The patients will be randomized into two groups: (1) early cholecystectomy (within 6 days after discharge) and (2) patients with delayed (interval) cholecystectomy (between 45 and 60 days after discharge). During a 12-month period, 93 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (that is, recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The secondary endpoints are organ failure, biliary leakage, technical difficulty of the cholecystectomy, surgical and other complications.

Ethics and dissemination. The trial has been registered at the ISRCTN (ref no. 10667869) and approved by the relevant organisation, the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Keywords: acute biliary pancreatitis, cholecystectomy, endoscopic sphincterotomy

Strengths and limitation

Strength 1: The study is designed as a prospective, randomized-controlled trial to achieve conclusion on the highest evidence level to provide the first evidence concerning the possible benefits of ES on timing cholecystectomy, it is (i) multinational (ii) multicentric, (iii) internationally registered and (iv) the pre-study protocol is published.

Strength 2: Only high volume, expert centers can join to the study. They have to provide (i) laparoscopically trained surgeons with >100 laparoscopic procedures performed and (ii) if ERCP/ES is provided during the index admission, trained gastroenterologist with >50 ES completed within a year must be on duty.

Strength 3: The study enjoys continuous support from (i) an International Translational Advisory Board (ITAB) including top, well-established experts from different are of research field (ii) an Independent Data Management Board (IDMB).

Strength 4: The final conclusion can be achieved with low number of patients within a relatively short period.

Limitation 1: The study will provide evidence in a selected population (mild ABP who underwent ERCP+ES) and no evidence concerning the usefulness of ES in moderate and severe ABP.

INTRODUCTION

Acute pancreatitis is one of the leading gastrointestinal causes of acute hospital admissions [1, 2]. In most cases, it is caused by gallstones, sludge or edema [3]. Gallstone-induced pancreatitis involves a pathophysiologic factor, namely a distal common channel of the biliary and pancreatic ducts, which can be found in 80% of acute biliary pancreatitis (ABP) [4]. Acute biliary pancreatitis is a clinical entity with high rates of morbidity (15–50%) and mortality (20–35%) [5]. After ABP, several complications may occur; recurrent acute pancreatitis, cholestasis and fistula affecting the hepatobiliary system or other biliary events, such as acute cholecystitis, obstruction of the common biliary duct, cholangitis or biliary colic [6, 7]. Interval cholecystectomy after mild ABP is associated with a high risk of readmission for recurrent biliary events, especially after recurrent ABP [8]. The international practice guidelines recommend that in case of cholangitis or choledocholthiasis an ERCP should be performed to clear the bile duct with endoscopic sphincterotomy (ES). In addition, cholecystectomy should also be performed to avoid complications related to recurrent biliary events [9, 10]. In patients with clinically severe pancreatitis, with local complications, such as pancreatic necrosis or organ failure, the intervention namely the laparoscopic cholecystectomy (LC) is delayed 6 months until complications are resolved [11]. In cases of mild ABP, cholecystectomy is recommended between days 7 and 21 [4]. The latest studies show that after discharge of patients with ABP, cholecystectomy could reduce the risk of a recurrent ABP and other gallstone-induced complications [12]. In this setting, surgeons still prefer delayed cholecystectomy for efficacy and safety and for logistical reasons [13]. Some publications draw attention to ERCP/ES, which could reduce mortality and the formation of severe biliary complications [3, 14]. The aim of the EMILY trial is to combine a surgical treatment and a gastroenterological procedure to investigate if ES with delayed cholecystectomy (within 45 to 60 days after discharge) compared with ES with early cholecystectomy (within 6 days after discharge) could reduce recurrent biliary events.

METHODS

Design: EMILY is a prospective, randomized-controlled, multicenter trial. The patients are randomized to two groups: (1) Patients who undergo early cholecystectomy (within 6 days after discharge) and (2) patients who undergo delayed (interval) cholecystectomy (between 45 and 60 days after discharge). During a 12-month period, 93 patients will be enrolled from participating clinics. The primary endpoint is a composite endpoint of mortality and recurrent acute biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic and cholangitis). The secondary endpoints are: organ failure, biliary leakage, technical difficulty of cholecystectomy, and surgical and other complications.

This study was structured following the SPIRIT 2013 [15] guideline defining standard protocol items for clinical trials and got the relevant ethical approval EKU/2018/12176-5 (Scientific and Research Ethical Committee, Medical Research Council, Hungary).

Trial organization, committees and boards: The coordinator and designer of the EMILY study is the Centre for Translational Medicine at the Universityof Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Pancreatic Study Group (HPSG-coordinating society, www.pancreas.hu). The HPSG was established in 2011 to stimulate research in pancreatic diseases.

Until now, it has launched three international observational clinical studies in 2014 [16, 17, 18] (EASY, APPLE and PINEAPPLE) and two interventional studies (PREPAST [19] – 2014 and GOULASH [20] – 2017) and has published the relevant guidelines for pancreatic diseases to improve patient care in pancreatology [21, 22, 23, 24].

The following committees and boards will be involved: Steering Committee (SC): The committee will be led by PH (corresponding investigator, gastroenterologist and internal medicine specialist).

The members in Szeged (HU) will be: LC (gastroenterologist), GL (surgeon); Debrecen (HU): MP (gastroenterologist), KP (gastroenterologist), ZS (surgeon); Pécs (HU): ÁV (gastroenterologist), DK (surgeon); Székesfehérvár (HU): FI (gastroenterologist), ÁA (surgeon); Targu Mures (RO): IT (gastroenterologist), LPK (surgeon); Cluj Napoca (RO): BS (surgeon), TM (gastroenterologist). KM is a trial management specialist, whereas AS leads the multidisciplinary core facility which will assist the scientists to run the study successfully. The SC will make decisions concerning all relevant questions including drop outs during the study.

International Translational Advisory Board (ITAB): The board will consist of a gastroenterologist (MML), a surgeon and two basic scientists (JN, MST, OHP). The ITAB will continuously monitor the progress of the study and will advise the SC.

The study was designed by the SC and ITAB. It was funded by the University of Pécs, Medical School. The sponsor was not involved in the design of the study, and will have no access to database or the randomization code.

The study also contains an independent physician and safety manager as required by the ethical regulation.

Study population: All patients with mild ABP (according to the revised Atlanta classification [25]) will be informed of the possibility to take part in the EMILY trial. After the consent form is signed participants will be randomized to 2 groups if they meet all the inclusion and no exclusion criteria (*Figure 1*).

Inclusion criteria: The criteria for inclusion in the study: (1) patients older than 18 years of age; (2) diagnosis of acute pancreatitis (at least 2 of the following 3 symptoms: upper abdominal pain, serum lipase or amylase is three times higher than the upper limit of normal and characteristic findings for acute pancreatitis on imaging); (3) the presence of ABP (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST; (4) mild ABP (meaning no pancreatic necrosis, no transient or persistent organ failure (>48 hours) is present; (5) ERCP/ES either during the index admission or in the medical history without complication (6) signed written informed consent (all included patient will sign the consent which contains the information about the trial and procedures) *(Figure 1)*.

Exclusion criteria: A patient's bad physical status can be an exclusion criterion. American Society of Anesthesiologists (ASA) III patients >75 years old; ASA IV or V patients, will be excluded. Patients with continuous alcohol abuse, acute or chronic cholecystitis during hospitalization, chronic pancreatitis, pregnancy, previous cholecystectomy will also be excluded *(Figure 1)*.

Time of randomization: 5 criteria are described by the PONCHO trial [26]. If these 5 criteria are met, the informed consent will be signed by the patient and a control abdominal CT will be carried out before discharge. These criteria are the following: (1) anticipation on the part of the treating physician that the patient can be discharged; (2) the patient has no abdominal pain and there is no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs. The patient must be randomized on the day of the discharge.

Randomization: The method of randomization is the following: The patient can be randomized by the study coordinator using a randomization module with sealed envelope. Patient data will be uploaded with the help of the administrator to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy *(Figure 1)*.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

Blinding: In prevention of patient's selection to group A and B trial participants, care providers and outcome assessors will be blinded until the allocation, as no access to randomization sequence. From assignment to intervention blinding cannot be provided

considering the study characteristics (exact date of cholecystectomy). The allocation sequence is unblinded only to data analysts who are completely independent form medical team (decision making) and data collection.

Endpoints

Primary endpoint. The primary endpoint is a composite endpoint, which is based on mortality and on recurrent biliary events (which are recurrent ABP, acute cholecystitis, uncomplicated biliary colic, and cholangitis). The observation period is three months. We decide based on criteria in *Figure 2* if a complication is present or not.

Secondary endpoints. We hypothesize that cholecystectomy for ABP between days 45-60 after discharge in patients with ES is as effective and safe as early cholecystectomy (within 6 day after discharge). In order to evaluate this, we will observe the following parameters: the number of biliary colic registered for the patient, difficulty of cholecystectomy (on a scale of 0-10, 0=easy, 5=moderately difficult, 10=hard, rate of conversion to open cholecystectomy, total length of hospital stay, need for ICU admission and total length of ICU stay, organ failure and biliary leakage *(Figure 2)*.

Treatment protocol

Randomization: Group A. Early cholecystectomy

Group B. Delayed cholecystectomy

We randomize patients into two groups after discharge *(Figure 3):*

Group A: The patient is randomized to the early cholecystectomy group, and cholecystectomy will be performed within 6 days after discharge.

Group B: The patient is randomized to the delayed cholecystectomy group, and the cholecystectomy will be carried out between 45 to 60 days.

Discontinuing or the modification of the allocated interventions for a trial participant is based on surgical causes like contraindicated opus, need for convertion to open cholecystectomy, or when the patient does not present to the hospital for cholecystectomy. Switching over the two interventions is not possible considering the trial characteristics, however in case of acute cholecystitis acute cholecystectomia can be performed independently from this trial. The case must be presented to SC.

Surgical details and quality control: If it will be the first ERCP/ES performed in the patient's medical history it will be performed according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines. [27] The laparoscopic cholecystectomy will follow the European Association Guidelines for Endoscopic Surgery [28]. The patients will be operated on by laparoscopically trained surgeons with >100 laparoscopic procedures performed and by a trained gastroenterologist with >50 ES completed within a year must be on duty if ERCP/ES is provided during the index admission. Centers which intend to randomize at least 15 patients and are able to perform an early cholecystectomy and ERCP/ES are eligible to participate in the study. In those centers which ES

data will then be collected on the incidence of choledocholithiasis, percentage bile duct injury, duration, and perceived difficulty (on a scale of 0-10).

Diagnosing and treating ABP: In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ERCP should be performed only in the case of cholangitis or choledocholthiasis, to clear the bile duct with endoscopic sphincterotomy (ES) as described in the IAP/APA guideline. When only the laboratory parameters suggest common bile duct obstruction or choledocholthiasis, MRCP/EUS should be carried out [10].

Data collection and follow-up: Data will be collected in a personalized database, and follow-up will consist of questionnaires *(Supplementary File)*. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator.

The personal information about enrolled participants will only be shared with IDMB as uploaded data for randomization, after data analysis only randomization code will be used for identification to protect confidentiality during, and after the trial. Only the principal investigator and the IDMB will have access to the final trial dataset. However only identification code is used, we can aside from duplicated patient's data as cholecystectomy can not be performed twice.

Sample size estimation method

Primary endpoint: a composite of gallstone-related complications or mortality occurring within 6 months after discharge.

Hypothesis: With regard to our hypothesis, based on a non-inferiority design, there is no difference between the two groups (5%) in mortality or readmission for gallstone-related complications within 3 months after discharge.

Starting point: Sample size estimation was based on the results obtained by the PONCHO trial carried out on 264 patients, where a non-significant difference of 14% was obtained between the two study groups (3% in the same-admission cholecystectomy group compared to 17% in the interval admission group). Thus, using the hypothesized 5% for the occurrence of the primary endpoint in the same-admission cholecystectomy group and a max difference of 14% given by the results of the PONCHO trial a total sample size of 93 was obtained using a 10% drop-out rate. The sample size estimation results are listed in the table below *(Figure 4)*.

Data management and statistical analyses: Data will be handled by an independent Clinical Research Organizer. Electronic CRF (eCRF) will be used. The Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager according to a Data Cleaning Plan (DCP). Adverse events will be coded using MedDRA according to GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements.

Safety Analysis Set (SAS, all patients enrolled in the study), Per Protocol Set (PPS, all enrolled patients who finished the study conforming to the requirements of the study protocol) and Intention to Treat (ITT, all randomized participants who start on a treatment, excluding consent withdrawals) will be performed.

Baseline patient and disease characteristics will be analyzed using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Descriptive statistics for both the primary and secondary parameters will be analyzed similarly.

Subgroup analyses will be perform concerning the imaging alterations (1: no gallstones or sludge on imaging, 2) sludge or 3) gallstone. Since we cannot exclude the possibility of fibrosis after earlier ES, we will perform a subgroup analysis during the interim analysis as well. If the results obtained from the interim analysis indicate that there could be significant difference between index admission and earlier ES, we will modify the trial protocol from the single-population (the same-admission endoscopic shicterotomy or ES in the medical history) two-arm (two groups: 1. Early cholecystectomy; 2. Delayed cholecystectomy) set up to a two-population two-arm set up (four groups: 1. early or 2. delayed cholecystectomy with index admission ES, 3. early or 4. delayed cholecystectomy in patients having earlier ES). The required patients' number will be adjusted in both populations accordingly. In case of important protocol modifications IDMB will report to the SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and national ethical committee http://www.ett.hu/tukeb.htm

Premature termination of the study: In the interests of patient safety, an interim analysis will be conducted after 15 patients and after half of the presumed number of patients (45) have completed the study. IDMB will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subjects' right, safety and well-being and to guarantee the plausibility of clinical data. Similarity of groups at baseline will be also checked. The study will also be stopped if the two groups' results differ significantly ($p<0.001$). The study will be discontinued if the difference between the planned number of patients and the actual number is higher than 60% within one year. IDMB will report to SC.

Centers: The trial will be launched in four Hungarian (Szeged, Debrecen, Pécs and Székesfehérvár) and two Romanian centres (Targu Mures and Cluj Napoca), after which the study will be open to other centres. In all cases, the IDMB will conduct an audit of the center and will report to the SC. The SC maintains the right to decide whether a center meets the required quality to join the study.

The full protocol will we available for public in an open access journal.

Publication policy: We would like to publish the results in one of the internationally highly recognized decent journals**.** Centers providing more than 25 patients can provide 4 authors to the authorship list: 2 surgeons and 2 gastroenterologists.

Patient and Public Involvement: This pre-study protocol contains no results and data, therefore patients and or public were not involved.

DISCUSSION

In the case of early laparoscopic cholecystectomy, while dissection and logistics are more difficult [6, 7] compared with delayed (interval) cholecystectomy, it is still more effective. Delayed cholecystectomy in a mild form of ABP is preferred by many surgeons, but a number of complications can occur: recurrent ABP, acute cholecystitis, obstruction of ductus choledochus, and uncomplicated biliary colic [6, 7]. After ERCP/ES is performed, the common bile duct is cleared, the complications caused by gallstones or sludge are significantly reduced [29]. The EMILY study is designed to determine if ERCP/ES for mild ABP aids in delaying the cholecystectomy to day 45-60 after discharge among patients with ABP.

If an ES aids in delaying a cholecystectomy, then we can reduce early cholecystectomy-related complications and the surgeons can proceed with a safer, easier cholecystectomy using this method of treatment.

ACKNOWLEDGEMENTS

Funding: Center costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs Medical School, Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00048 Stay Alive, KH-125678 and EFOP 3.6.2-16-2017-00006 Live Longer), and Translational Medicine Foundation.

Since no additional treatment is necessary for the study, the general healthcare costs are covered by the National Healthcare System (University of Pécs-Medical School).

This study was designed with help of the Centre for Translational Medicine at the University of Pécs. This center is committed to improve patient's life with research activities like registries, observational and interventional trial organizations (https://tm-centre.org).

There are no financial and other competing interests for principal investigators (LPK, DK), included patients or any member of the trial.

AUTHORS' CONTRIBUTION

LPK, KM, DK, ÁV, LC, MP, FI, ÁA, MT and PH designed the study. As a member of the ITAB MML, JN, MST and OHP gave advices and will continuously monitor the progress of the study. LPK, KM, PH, ZsSz, KP drafted the manuscript, GyL, SB, AV, LB, MD, NZ, JA and ASz edited the manuscript. IN carried out the sample size calculation. ZsSz, KP, IT, NZ, JA, ASz edited the figures and tables. All authors read and approved the final manuscript.

During the study IT, ÁV, LC, MP and MT are going to manage the endoscopic treatments. DK, GyL, ZsSz, MD and SB are responsible for cholecystectomies. ITAB and SC members are listed ahead.

Competing interests statement: All authors declare no competing interests.

ETHICS AND DISSEMINATION

Trial registration: The trial has been registered at the ISRCTN10667869.

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (EKU/2018/12176-5).

Protocol Version: V1.0 10.07.2018.

Start of the patient recruitment: 1st March 2019

Additional information and future plan: Blood samples (serum and plasma) will be stored from all patients in order to study laboratory parameters later if required (e.g. the laboratory could not measure it), and in order to build up a biobank for later clinical studies to which all participants will give informed consent. The samples will be stored at -80°C.

The post-trial care will follow the routine tratment protocols. In case if patient suffer a harm during hospitalization all of the responsability is taken by the hospital where the patient is treated.

LIST OF ABBREVATIONS

ABP – acute biliary pancreatitis

ASA – American Society of Anesthesiologists

CECT – contrast enhanced computed tomography

DCP – Data Cleaning Plan

DMP – Data Management Plan

ES – endoscopic shicterotomy

eCRF – electronic case report form

ESGE – European Society of Gastrointestinal Endoscopy

HPSG – Hungarian Pancreatic Study Group

IDMB – Independent Data Management Board

ITAB – International Translational Advisory Board

ITT – Intent to Treat

LC – Laparoscopic cholecystectomy

PPS – Per Protocol Set

SAS – Safety Analysis Set

SC – Steering Comittee

References

1. Peery AF, Dellon ES, Lund J, Crockett SD, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179–87. doi: 10.1053/j.gastro.2012.08.002

2. Dhiraj Y, Albert BL. The epidemiology of pancreatitis and pancreatic cancer gastroenterology. Gastroenterology 2013;144(6):1252–1261. doi: 10.1053/j.gastro.2013.01.068

3. Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. Schepers et al. Trials 2016;17:5. doi: 10.1186/s13063-015-1132-0

4. Uhl W, Müller CA, Krähenbühl L et al. Acute gallstone pancreatitis, Timing of laparoscopic cholecystectomy in mild and severe disease. SurgEndosc 1999;13:1070–1076

5. Schietroma M, Carlei F, Lezoche E, et al. Acute biliary pancreatitis: staging and management. Hepato-gastroenterology 2001;48(40):988–993

6. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl 3):iii1–iii9. doi: 10.1136/gut.2004.057026

7. Forsmark CE, Baillie J. AGA institute technical review on acute pancreatitis. Gastroenterology 2007;132:2022–2044. doi: 10.1053/j.gastro.2007.03.065.

8. van Baal MC, Besselink MG, Bakker OJ, et al. for the Dutch Pancreatitis Study Group: Interval cholecystectomy after mild biliary pancreatitis is associated with a high risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. Annals of Surgery 2012;255(5):860–866. doi: 10.1097/sla.0b013e3182507646

9. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400. doi: 10.1111/j.1572-0241.2006.00856.x.

10. Uhl W, Warshaw A, Imrie C, et al. IAP Guidelines for the Surgical Management of Acute Pancreatitis. Pancreatology 2002;2:565–573. doi: 10.1159/000067684

11. Nealon WH, Bawduniak J, Walser EM. Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. Ann Surg 2004;239:741–749. doi:10.1097/01.sla.0000128688.97556.94

12. da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicenter randomized controlled trial. Lancet 2015;386:1261–68. doi: 10.1016/s0140-6736(15)00274-3

13. Paul GL, Bettina WD, Markus ML. Clinical perspectives in pancreatology: Compliance with Acute Pancreatitis Guidelines in Germany. Pancreatology 2005;5:591–593. doi: 10.1159/000087501

14. Uomo G, Manes G, Laccetti M, et al. Endoscopic sphincterotomy and recurrence of acute pancreatitis in gallstone patients considered unfit for surgery. Pancreas 1997;14:28–31.

15. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583

16. Hritz I, Hegyi P. Early Achievable Severity (EASY) index for simple and accurate expedite risk stratification in acute pancreatitis. J Gastrointestin Liver Dis 2015;24(2):177–82. doi: 10.15403/jgld.2014.1121.242.easy

17. Párniczky A, Mosztbacher D, Zsoldos F et al. Analysis of Pediatric Pancreatitis (APPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):105–10. doi: 10.1159/000441353

18. Zsoldos F, Párniczky A, Mosztbacher D, et al. Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-study protocol of a multinational prospective clinical trial. Digestion 2016;93(2):121–6. doi: 10.1159/000441352

19. Dubravcsik Z, , Madácsy L, Gyökeres T, et al. Preventive pancreatic stents in the management of acute biliary pancreatitis (PREPAST trial): pre-study protocol for a multicenter, prospective, randomized, interventional, controlled trial. Pancreatology 2015;15(2):115–23. doi: 10.1016/j.pan.2015.02.007

20. Márta K, Szabó AN, Pécsi D, et al. High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open 2017;7(9):e015874. doi: 10.1136/bmjopen-2017-015874

21. Dubravcsik Z, Farkas G, Hegyi P, et al. [Autoimmune pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):292–307. doi: 10.1556/OH.2015.30061

22. Hritz I, Czakó L, Dubravcsik Z, et al. [Acute pancreatitis. Evidence-based practice guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):244–61. doi: 10.1556/OH.2015.30059

23. Parniczky A, Czakó L, Dubravcsik Zs, et al. [Pediatric pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(8):308–25. doi: 10.1556/OH.2015.30062

24. Takacs T, Czakó L, Dubravcsik Z, et al. [Chronic pancreatitis. Evidence-based management guidelines prepared by the Hungarian Pancreatic Study Group]. Orvosi Hetilap 2015;156(7):262–88. doi: 10.1556/OH.2015.30060

25. Banks, P.A., et al., Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut, 2013. 62(1): p. 102-11.

26. Bouwense SA, Besselink MG, van Brunschot S, et al. Pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial): study protocol for a randomized controlled trial. Published online 26 Nov 2012. doi: 10.1186/1745-6215-13-225

27. Pier AT, Alberto M, Lars A, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016 Jul;48(7):657-83. doi: 10.1055/s-0042-108641

28. Edmund AMN, Hans T, CK Kum, et al. EAES Clinical Practice Guidelines on Laparoscopic Cholecystectomy, Appendectomy, and Hernia Repair (1994). In: EAES guidelines for endoscopic surgery: Twelve years evidence-based surgery in Europe. E. Neugebauer, S. Sauerland, A.B. Fingerhut, B. Millat, G.F. Buess (Eds.). Springer Berlin Heildelberg, 2006:265-289

29. Testoni PA. Acute recurrent pancreatitis: Etiopathogenesis, diagnosis and treatment. World J Gastroenterol 2014;20(45):16891. doi: 10.3748/wjg.v20.i45.16891

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline [15]

** no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1) diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST*

*** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old*

Figure 2 Shows the evaluation of primary and secondary endpoints.

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15].

**Diagnosis of acute biliary pancreatitis (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST. In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ABP is mild, when there is no pancreatic necrosis, or no transient or persistent organ failure (>48 hours).*

***If it is necessary to perform endoscopic sphincterotomy during the current admission or ES in the medical history also acceptable.*

**** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q5, Q7, Q8, Q=question)*

***** The patient can be randomized by using a randomization module with sealed envelope. Patient data will be uploaded to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy.*

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

****** The criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or*

systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs; and (6) ERCP/ES either during the index admission or in the medical history without complication. Before discharge or transfer to surgery department.

Figure 4 The listed parameters were used to estimate results for the current sample size.

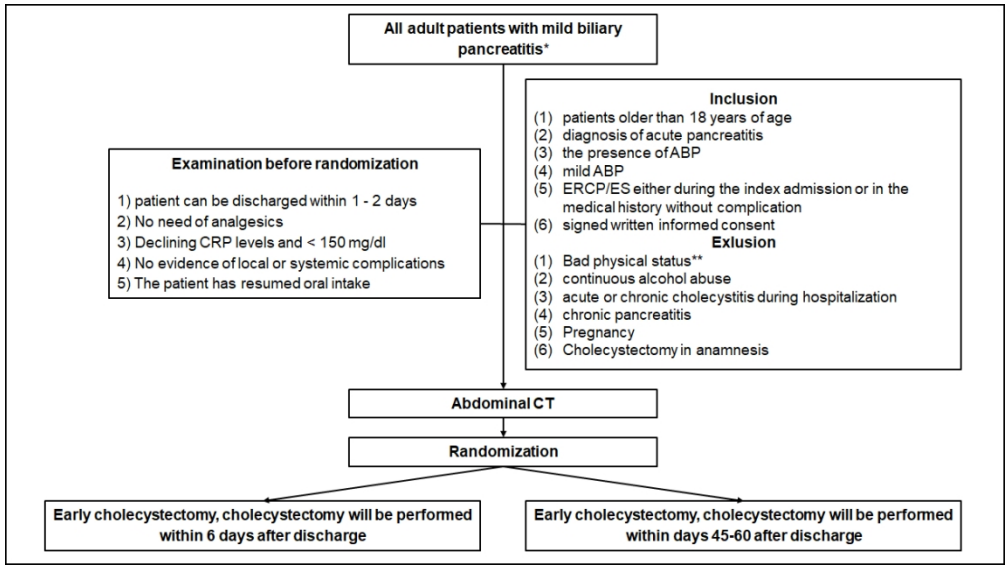

Figure 1 Shows the flow chart of participants according to SPIRIT 2013 guideline [15]
* no pancreatic necrosis, no transient or persistent organ failure (>48 hours)) is present with any of the following 3 definitions: 1) diagnosis of gallstones or sludge on imaging, 2) a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder, 3) and alanine aminotransferase level >2 times higher than normal values with ALT > AST
** American Society of Anesthesiologists (ASA) IV or V patients and ASA III >75 years old

105x59mm (300 x 300 DPI)

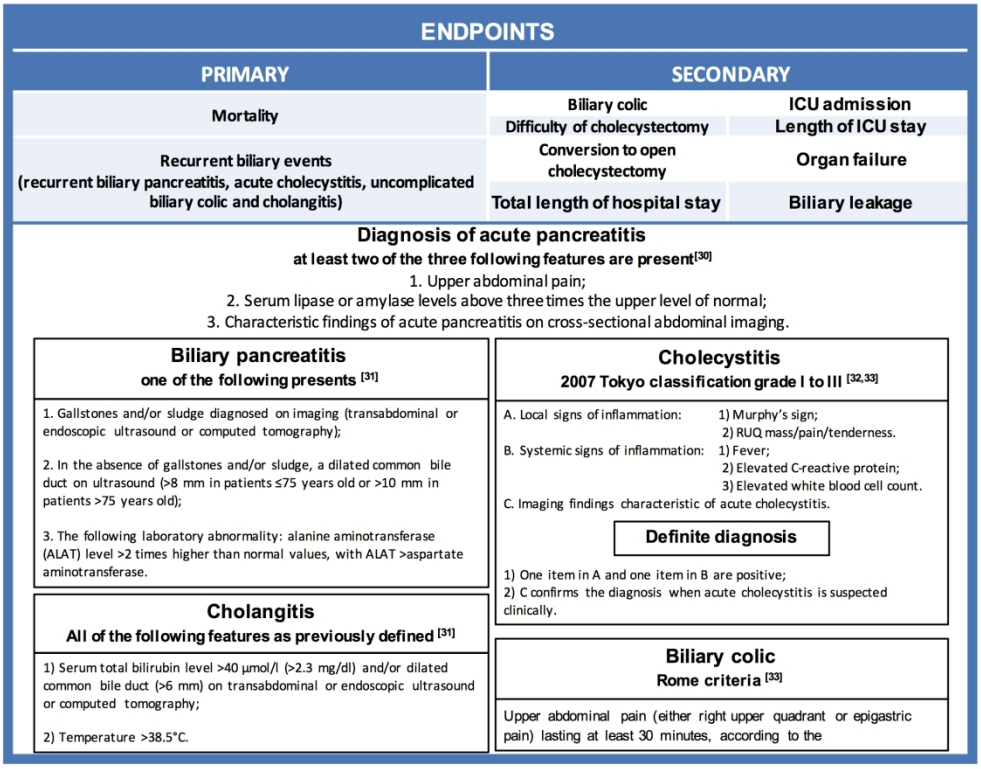

Figure 2 Shows the evaluation of primary and secondary endpoints.

198x154mm (300 x 300 DPI)

STUDY PERIOD							
DIVISION	Gastroenterology management				Department of Surgery		Control visit
SERVING	DOCTOR no.1 and no.2				DOCTOR no.3		DOCTOR no.4
	1	1	2	1			
OBJECT	MBP management and randomization				Cholecystectomy after discharge		Follow up
TIMEPOINT	– several days	0		+ several days	Within 6 days	Between day 45-60	Day 90±7 after discharge
ENROLMENT:							
Diagnosis of acute mild biliary pancreatitis*	X						
ES**		X					
Eligibility screen			X Q2-4				
TEST 1***				X Q5			
Sign of Informed consent form				X Q6			
Allocation****				X Q6			
Randomization****				X Q6			
Discharge***** to home or to surg.				X			
INTERVENTIONS:							
Group A Early cholecystectomy					X		
Group B Delayed cholecystectomy						X	
TEST 2***					X Q7	X Q7	
ASSESSMENTS:							
Follow up (with the help of an administrator***							X Q8

Figure 3 Schedule of enrolment, interventions and assessments according to the SPIRIT 2013 statement [15].

*Diagnosis of acute biliary pancreatitis (any of the following 3 definitions): diagnosis of gallstones or sludge on imaging, a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old) in the absence of gallstones or sludge in the gallbladder; and alanine aminotransferase level >2 times higher than normal values with ALT > AST. In the first 24 hours of admission, all patients will undergo either an ultrasonography or a contrast-enhanced computed tomography (CECT) to detect if the gallbladder contains gallstones or sludge and to determinate the diameter of the common bile duct. ABP is mild, when there is no pancreatic necrosis, or no transient or persistent organ failure (>48 hours).

**If it is necessary to perform endoscopic sphincterotomy during the current admission or ES in the medical history also acceptable.

*** Data will be collected in a personalized database, and follow-up will consist of questionnaires. The patient will be asked to note every biliary event during the follow-up period and will be contacted in person within the 90 days after discharge to collect information. After data collection, we can draw conclusions about the treatment strategy. Improperly completed datasheets and incorrect data upload will be avoided and controlled by the administrator. (Q5, Q7, Q8, Q=question)

**** The patient can be randomized by using a randomization module with sealed envelope. Patient data will be uploaded to the data base, which will be followed by the randomization. This randomization module will allocate the participants to the 2 different groups. This method makes it impossible for researchers to predict the allocation of the patients involved in the study. It is impossible to conceal the distribution of the patients in this study because the patients need to be scheduled for either an early cholecystectomy or a delayed cholecystectomy.

Allocation will be carried out based on predefined randomisation lists created separately for each recruiting centre. The allocation sequence will be prepared with a block size of 4 and with an allocation ratio 1:1 by the Independent Data Management Board (IDMB).

***** The criteria are the following: (1) Anticipation on the part of the treating physician that the patient can be discharged within 1 or 2 days; (2) no need for analgesics; (3) declining C-reactive protein levels and <150 mg/l; (4) no evidence of local or systemic complications (for example, no fever); (5) oral feeding is tolerated for 24 hrs; and (6) ERCP/ES either during the index admission or in the medical history without complication. Before discharge or transfer to surgery department.

108x61mm (300 x 300 DPI)

Hypothesised proportion in each group	Significance level	Power	Acceptable max. difference for equivalency	Sample size needed for analysis (per group)	Sample size for screening (with 5% drop-out rate)
5%	95%	90%	14%	42	89

Figure 4 The listed parameters were used to estimate results for the current sample size.

271x39mm (300 x 300 DPI)

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY
HUNGARIAN PANCREATIC STUDY GROUP

QUESTIONNAIRE

1. Personal data

1.1 Patient's data

Name:_____ Sex: Male / Female

Date of Birth:_____Age:_____ Insurance number:__

_____

Phone number:_____ The patient's study number:

1.2 Doctors' data

DOCTOR No. 1:

Name of the doctor **responsible for the treatment of ABP**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 2:

Name of the doctor **responsible for the randomization**:_____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 3:

Name of the doctor **responsible for the operation**: _____

The phone number of the doctor:_____

Institute: _____

DOCTOR No. 4:

Name of the doctor **responsible for the 90 days' visit**: _____

The phone number of the doctor:_____

Institute: _____

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

2. Inclusion criteria /DOCTOR No. 2/

Patients older than 18 age	**YES**	**NO**
Diagnosis of acute pancreatitis (two of them have to be positive) - upper abdominal pain - serum lipase or amylase is three times higher of upper limit of normal - characteristic findings of acute pancreatitis on abdominal imaging	**YES**	**NO**
Presence of biliary pancreatitis (one of them has to be true) - diagnosis of gallstone or sludge on imaging - the absence of gallstone or sludge with a dilated common bile duct on ultrasound (>8 mm in patients ≤75 years of age or >10 mm in patients >75 years old) - alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Mild acute biliary pancreatitis (all of them have to be true) /HAS TO BE DETERMINED AT DISCHARGE OF THE PATIENT/ - no peripancreatic fluid collections - no pancreatic necrosis - no persistent organ failure	**YES**	**NO**
ERCP/ES either during the index admission or in the medical history without complication	**YES**	**NO**
Written informed consent	**YES**	**NO**
One „NO" is present = DO NOT INCLUDE!		

3. Exclusion criteria /DOCTOR No. 2/

American Society of Anesthesiologists (ASA) classification - III patients >75 years old - IV, V, VI. Groups	**YES**	**NO**
Acute or chronic cholecystitis during hospitalization	**YES**	**NO**
Previous cholecystectomy	**YES**	**NO**
Continuous alcohol abuse or chronic pancreatitis	**YES**	**NO**
Pregnancy	**YES**	**NO**
One „YES" is present = EXCLUDE!		

4. If all inclusions and no exclusion criteria are met, than the physician may indicate the patient to participate in the study. / DOCTOR No. 2/

The treating physician (DOCTOR No. 2) anticipates that the patient can be discharged	**YES**	**NO**
No need for analgesics	**YES**	**NO**
Declining C-reactive protein levels and <150 mg/l	**YES**	**NO**
No evidence of local or systemic complications	**YES**	**NO**
The patient has resumed solid oral nutrient	**YES**	**NO**
If all YES = RANDOMIZATION /see point 6/		

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

5. Medical History and characteristics of ABP / DOCTOR No. 1/

Date of admission (diagnosis of AP):……

Date of discharge: ……

5.1 Anamnesis

History of upper abdominal surgery: Yes / No
If yes, interventions:……
……
History if biliary colics Yes / No
History of cholecystitis Yes / No
Fever Yes / No .....°C
Diabetes Yes / No
Antibiotic therapy during the ABP Yes / No

BMI Weight:_____kg, Height:_____cm, BMI:_____kg/m^2

ASA classification (ASA PHYSICAL STATUS CLASSIFICATION SYSTEM)

I. group(**Normal** healthy patient)	**YES**	**NO**
II. group(Patient with **mild systemic disease** with no functional limitations)	**YES**	**NO**
III. group(Patient with **moderate** systemic disease **with functional limitations**)	**YES**	**NO**

5.2. Laboratory measurements

At discharge after AP:

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alkaline phosphatase(U/l)	

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

5.3. Pancreatic imaging /At discharge after AP/

5.3.1 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

Please NOTE! Abdominal CT is compulsory when the patient is discharged

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:** ☐
- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**.....cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area .....cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter .....cm)
  - Both sides, L - ……. cm, R .....cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: …….
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: …….
  - none

Other Description:
……
……
……
……

5.4. Characteristics of AP

Date of diagnosis (admission)……..……

Date of EST:…….

Date of discharge: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

6. Randomization / DOCTOR No. 2/

The patient will be randomized by an internet randomization module in the following 2 groups:

Randomization:

A. Early cholecystectomy (within 6 days after discharge)

B. Delayed cholecystectomy (between 45 and 60 days after discharge)

Please circle the relevant group after randomization: A or B

Please inform the patient concerning the **1)** Date for imaging examination and blood measurements before the operation, **2)** Date for the operation, **3)** Date for the 90 days visit

7. Operation /responsibility of DOCTOR No. 3/

Date of operation: ……

Length of days between discharge and operation: ……

If the operation is not in the time period described in point 6 please provide the reason: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.1 Anamnesis (between discharge after ABP and operation)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis** 1) One item in A and one item in B are positive; 2) C confirms the diagnosis when acute cholecystitis is suspected clinically	**YES**	**NO**
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers is **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reasons for hospitalization: ……

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.2 Laboratory measurements (no more than 24h before the operation)

Amylase(U/l)		Hematocrit(%)	
Lipase(U/l)		Hemoglobin(g/l)	
Gamma GT(U/l)		Kreatinine(umol/l)	
White blood cell(G/l)		eGFR	
ASAT/GOT(U/l)		CRP(mg/l)	
INR(U/l)		Alcaline phosphatase(U/l)	

If the patient is in group A, and the operation is performed within 24h after the blood samples are taken during the discharge of the patients, NO ADDITIONAL BLOOD SAMPLE HAS TO BE TAKEN. Please copy the values from 5.2.

7.3 Pancreatic imaging

7.3.1 Abdominal ultrasonography:

- ***Visualization:***
  - Good, complete (head at least partially visualized, body and neck well visualized, tail: partially visualized)
  - Partially, incomplete (only body or only head visualized)
  - Poor, non-diagnostic
- **Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)

- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm

- **Pancreas homogeneity:**
  - Homogenous
  - Inhomogeneous, includes area(s) of low echogenicity
  - Inhomogeneous, includes calcifications

- In case of circumscribed low echogenicity area, it's size.....cm

- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)

Other Description:
.....
.....
.....

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.3.2 Abdominal Computed Tomography: yes/no
Modified CTSI Score (0-10): ……

CTSI Score: (I) Normal pancreas 0 point, intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat 2 points, Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis 4 points **(II)** Necrosis absent 0 Points, < 30% necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of extrapancreatic findings 2 points.
MAXIMUM OF: 10 points

- **CTSI:** ☐
- **Pancreas Size:**
  - Normal
  - Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)
  - Definitely enlarged (any part over 3 cm AP diameter)
- Largest diameter of peripancreatic **fat infiltration**.....cm
- **Peripancreatic fluid:**
  - none
  - present
  - Large pseudocyst(s)
- Size of peripancreatic fluid or pseudocyst: .....cm
- **Necrotizing area** (nonenchancement):
  - Largest diameter of necrosis area .....cm
  - Location of necrosis: ……
  - Type: patchy / full width
  - Estimated necrosis: 0%, < 30% , 30% - 60%, > 60%
- **Wirsung** dilatation: YES / NO (yes, diameter.....mm)
- Distant **abdominal fluid**:
  - Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)

- Moderate amount (easy to see, but without pelvic or abdominal distension)
- Large amount with abdominal/pelvic distension

- **Pleural effusion:**
  - none
  - one sided:……. (AP diameter .....cm)
  - Both sides, L - ……. cm, R .....cm
- **Extrapancreatic findings**:
  - Inflammation (Cholecystitis, Duodenitis, etc.) location: …….
  - Cholecystolithiasis
  - Choledocholithiais
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: …….
  - none

Other Description:
……
……
……
……

If the patient is in group A, and the operation is performed within 24h after the imaging is performed during the discharge of the patients, NO ADDITIONAL IMAGING EXAMINATION HAS TO BE ORDERED. Please copy the details from 5.3.

Endoscopic sphincteroto**M**y for delay**I**ng
cho**L**ecystectomy in mild acute biliar**Y** pancreatitis

TMEMILY HUNGARIAN PANCREATIC STUDY GROUP

7.4. Characteristics of the Operation

The dificulty of cholecystectomy(10 – hard, 5 – average difficulty):

1	2	3	4	5	6	7	8	9	10

Conversion to open cholecystectomy: Yes / No
The lenght of the operation (min):_____
Days spent in hospital after cholecystectomy:_____
Intenziv unit care: Yes / No
Mortality: Yes / No
Haemorrhage, reintervention needed: Yes / No
No Iatrogenic perforation of the gallbladder Yes / No
Common bile duct (CBD) injuries Yes / No
Bile leakage Yes / No
Sub-hepatic abscess Yes / No

8. Visit 90 days after discharge / DOCTOR No. 4/

The visit has to be completed +/- 7 days (between 83 and 97 days after discharge)

Date of the visit: ……

Length of days between discharge and visit: ……

8.1 Anamnesis (between the operation and visit)

Acut pancreatitis - Upper abdominal pain - Serum lipase or amylase is three times higher of upper limit of normal - Characteristic findings of acute pancreatitis on cross-sectional abdominal imaging	**YES**	**NO**
Biliary pancreatitis - Diagnosis of gallstone or sludge on imaging - Dilated common bile duct on ultrasound (>8 mm in patients ≤75 years old or >10 mm in patients >75 years old - Alanine aminotransferase level >2 times higher than normal values	**YES**	**NO**
Cholecystitis A. Local signs of inflammation: 1) Murphy's sign; 2) RUQ mass/pain/tenderness. B. Systemic signs of inflammation: 1) Fever; 2) Elevated C-reactive protein; 3) Elevated white blood cell count. C. Imaging findings characteristic of acute cholecystitis **Final diagnosis**	**YES**	**NO**

Endoscopic sphincterototo**M**y for delay**I**ng
Long-term **A**nd **I**dem in **B**ile **Y** positive

1) cholecystectomy in mild acute biliary pancreatitis 2) C confirms the diagnosis when acute cholecystitis is suspected clinically		
Biliary colics Upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30 minutes, according to the Rome criteria	**YES**	**NO**
Cholangitis 1) Serum total bilirubin level >40 µmol/l (>2.3 mg/dl) and/or dilated common bile duct (>6 mm) on transabdominal or endoscopic ultrasound or computed tomography; 2) Temperature >38.5°C.	**YES**	**NO**
Organ failure 1) Respiratory: PaO2 ≤60 mmHg (SaO2 ≤ 90%) or need for mechanical ventilation; 2) Cardiovascular: systolic blood pressure <90 mmHg or need for catecholamine support; 3) Renal: creatinine level >177 µmol/l after rehydration or need for hemofiltration or hemodialysis (not including pre-existent renal failure).	**YES**	**NO**
Mortality	**YES**	**NO**

If any of the answers **YES** please provide the dates: ……

Except mortality, all of the above mentioned diseases can occure multiple times. Please provide details for all events separately.

Other reason for hospitalization: ……

SIGNATURES:

Doctor No.1…….. **Date:……..**

Doctor No.2…….. **Date:……..**

Doctor No.3…….. **Date:……..**

Doctor No.4…….. **Date:……..**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Description	Addressed on page number
Administrative information		
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	3
	All items from the World Health Organization Trial Registration Data Set	–
Protocol version	Date and version identifier	10
Funding	Sources and types of financial, material, and other support	10
Roles and responsibilities	Names, affiliations, and roles of protocol contributors	1, 10
	Name and contact information for the trial sponsor	5, 10
	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	5
	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)	4,5, 8-9
Introduction		
Background and rationale	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	4
	Explanation for choice of comparators	4,8,9
Objectives	Specific objectives or hypotheses	5, 8

1

Trial design	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes		
Study setting	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	5,8-9
Eligibility criteria	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7-8
	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	Relevant concomitant care and interventions that are permitted or prohibited during the trial	–
Outcomes	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	7
Participant timeline	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig.3
Sample size	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	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	6

Allocation concealment mechanism	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	6
Implementation	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	–
Methods: Data collection, management, and analysis		
Data collection methods	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	8
	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	8
Data management	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	8-9
Statistical methods	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	8
	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring		

Data monitoring	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	8-9
	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	9
Harms	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8-9
Auditing	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination		
Research ethics approval	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,10
Protocol amendments	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)	9
Consent or assent	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10-11
Confidentiality	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	8
Declaration of interests	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Access to data	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10-11
Dissemination policy	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	9
	Authorship eligibility guidelines and any intended use of professional writers	9
	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	9
Appendices		
Informed consent materials	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	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	10-11

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.