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Recurrent acute pancreatitis prevention by the elimination of alcohol and cigarette smoking (REAPPEAR): protocol of a randomised controlled trial and a cohort study

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ABSTRACT

Background/objectives Acute recurrent pancreatitis (ARP) due to alcohol and/or tobacco abuse is a preventable disease which lowers quality of life and can lead to chronic pancreatitis. The REAPPEAR study aims to investigate whether a combined patient education and cessation programme for smoking and alcohol prevents ARP.

Methods and analysis The REAPPEAR study consists of an international multicentre randomised controlled trial (REAPPEAR-T) testing the efficacy of a cessation programme on alcohol and smoking and a prospective cohort study (REAPPEAR-C) assessing the effects of change in alcohol consumption and smoking (irrespective of intervention). Daily smoker patients hospitalised with alcohol-induced acute pancreatitis (AP) will be enrolled. All patients will receive a standard intervention priorly to encourage alcohol and smoking cessation. Participants will be subjected to laboratory testing, measurement of blood pressure and body mass index and will provide blood, hair and urine samples for later biomarker analysis. Addiction, motivation to change, socioeconomic status and quality of life will be evaluated with questionnaires. In the trial, patients will be randomised either to the cessation programme with 3-monthly visits or to the control group with annual visits. Participants of the cessation programme will receive a brief intervention at every visit with direct feedback on their alcohol consumption based on laboratory results. The primary endpoint will be the composite of 2-year all-cause recurrence rate of AP and/or 2-year all-cause mortality. The cost-effectiveness of the cessation programme will be evaluated. An estimated 182 participants will be enrolled per group to the REAPPEAR-T with further enrolment to the cohort.

Ethics and dissemination The study was approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council (40394-10/2020/EÜIG), all local ethical approvals are in place. Results will be disseminated at conferences and in peer-reviewed journals.

Trial registration number NCT04647097

Strengths and limitations of this study

- This is the first study assessing a combined brief intervention programme for recurrence prevention in acute pancreatitis.
- The study could provide a cost-effective and easy-to-use preventive method, reducing the recurrence rate of alcoholic acute pancreatitis.
- The lack of a conventional control group could result in underestimating the efficacy of the cessation programme.
- The results will be specific to the enrolled patient population, which does not cover all patients with recurrent acute pancreatitis.

INTRODUCTION

Acute pancreatitis (AP) is an often-unheeded issue by clinicians and healthcare professionals, with significant medical charges.[1 2] The incidence rate of the first attack of AP ranges from 15 to 45 per 100 000 per year.[3] Alcohol and biliary obstruction are the two main causes of AP in adulthood, alcohol being the diagnosed inducing factor in 25%–35% of the cases.[4]

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Cohort studies have found that 10%–30% of patients have recurrent attacks based on medical history, and a recent meta-analysis has shown that 10% of the patients after a single episode of AP and 26% of those with acute recurrent pancreatitis (ARP) later progress to chronic pancreatitis (CP).[5] It Is known, that ARP (more than one episodes of AP) significantly lowers physical and mental quality of life (QoL)[6] and alcoholic aetiology has been identified in 19% of ARP patients.[7] Despite the importance and potentially preventable nature of alcoholic ARP, preventive efforts are still scarce.[8 9]

A pivotal study from Nikkola *et al* found that abstinent patients experienced no ARPs during a 9-year follow-up period. On the other hand, 34% of patients who did not stop drinking developed a recurrent attack.[10] The median time between the index AP and the first alcoholic ARP ranges from 8.5 months to 2.2 years, but around 80% of the registered first recurrent attacks occur in the first 4 years of follow-up.[11 12] With 6-monthly interventions, Nordback *et al* achieved a significant reduction in the recurrence rate of AP in Finland.[13 14]

Smoking is a long-established independent risk factor of AP and CP. A dose–response association was found between smoking and AP,[15 16] and combined with heavy drinking, smoking can further increase the risk of AP up to four times compared with non-smokers.[17 18] Findings are controversial regarding the effects of smoking cessation. A study published by Sadr-Azodi found that the risk of AP is statistically comparable to never-smokers' after 20 non-smoking years.[17] In contrast, a meta-analysis showed an elevated risk of AP in former smokers compared with never-smokers.[18]

Limiting alcohol use and smoking apart from their positive effects on the pancreas generally improve health[19] and up to a certain extent, organ damage caused by these substances is reversible.[20–23] Smoking cessation alone can prolong life with 1.4–8.5 years.[24]

In a Hungarian cohort study of 600 patients, alcohol consumption was four times more frequent in males, alcoholic aetiology represented 26.5% of all cases and was often associated with smoking. Alcoholic ARP accounted for 21.2% of all cases in the cohort.[25] In a CP cohort, daily alcohol consumption, as an etiological factor, was present in 56% of the cases, and 56% of the participants smoked more than 10 cigarettes/day.[26]

It is known that more than half of patients suffering from alcohol use disorder (AUD) are also dependent on tobacco, and that continued tobacco use represents a more than two-fold risk for relapse.[27 28] To this day, there are no adjusted protocols for the treatment and follow-up of heavy-drinking smokers.[29 30] It is proven that, in contrast with previous assumptions, smoking cessation programmes for patients at risk or living with AUD improve alcohol-related outcomes[27 31] and a brief alcohol intervention improves the rate of successful smoking cessation.[32]

However, to date, no study has examined the effects of a combined intervention for the reduction of nicotine and alcohol consumption in ARP and guidance is very limited on this topic,[33–36] (online supplemental table S1). Based on the above-mentioned reasons, while all patients with alcoholic AP should receive counselling, a one-time brief intervention will be provided to all participants, without further counselling in the control group.

Objectives

The study encompasses a randomised controlled trial (RCT) (REAPPEAR-T: Recurrent acute pancreatitis prevention by the elimination of alcohol and cigarette smoking; trial) and a concomitant cohort study (REAPPEAR-C: Recurrent acute pancreatitis prevention by the elimination of alcohol and cigarette smoking; cohort). The REAPPEAR-T's objective is to investigate the effect of an alcohol and smoking cessation programme combined with patient education on the recurrence rate of alcohol-induced AP, CP and QoL. Additionally, the REAPPEAR-C's objective is to investigate the effect of alcohol and smoking cessation (irrespective of intervention) on the recurrence rate of alcohol-induced AP, CP and QoL.

METHODS

Design

The REAPPEAR study, designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement,[37] uses a combined design to answer two questions in one particular patient population. The REAPPEAR-T will be an international, single-blind, two-arm, parallel group, superiority RCT, testing the efficacy of a cessation programme for alcohol and smoking, using brief interventions. The REAPPEAR-C is a prospective four-arm cohort study, which includes all patients participating in REAPPEAR-T with further enrolment after the termination of enrolment to the trial. In the cohort, patients will be grouped by smoking status and alcohol consumption at the end of the study, irrespective of intervention. The same eligibility criteria and outcomes will be used in both substudies and differences will be described in the appropriate sections in detail.

The study will be conducted in Hungary, Ukraine, Italy and Romania (list of centres in online supplemental file 1). Centres are welcome to join. The enhance the visibility of this project and centre recruitment, the protocol is being presented on national and international conferences. Patients will be enrolled during their hospitalisation for AP and will be followed during ambulatory visits to the same hospital.

Population

Inclusion criteria

- Patient hospitalised with alcohol-induced AP (defined by the revised Atlanta criteria.[38]
- Regular consumption of at least 40 g (women)/ 50 g (men) alcohol daily or 280 g (women)/ 350 g (men) alcohol during the preceding week of onset of abdominal pain

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- Every day smoker (defined as an adult patient who smoked at least 100 cigarettes in his or her lifetime, and now smokes on a daily basis; as per the CDC definition), with at least 1-year history of smoking.
- Aged 18–65 years.[39]
- Completed the standard intervention (SI) (see below).
- Provided written informed consent (online supplemental file 2).

Exclusion criteria

- Possible aetiologies for AP other than alcohol (eg, gallstone-related, hypertriglyceridaemia above 11.5 mM,[40–42] hypercalcaemia, viral infection) and cases with combined etiological factors will be excluded.
- Major psychiatric illnesses (eg, schizophrenia, bipolar disorder, dementia).
- Currently receiving therapy for AUD.
- Currently taking part in a smoking cessation programme.
- Three or more documented lifetime episodes of AP.[43]
- CP.[44]
- Undergoing active or palliative treatment for malignancy.
- Pregnancy.
- Life expectancy is less than 2 years.

Medical personnel not involved in the treatment of the patient will perform formal screening and obtain informed consent.

Standard intervention

The SI will be incorporated into standard medical therapy in all centres, and will be provided to all patients hospitalised for alcohol-induced AP. SI will be delivered by a specially trained nurse because interventions delivered by nurses have been found to be the most effective in reducing the quantity of alcohol consumed.[45] The intervention will be based on the WHO initiative 'Assist-linked brief intervention', using psychoeducational and motivational interviewing techniques.[46] For SI, we calculated with an average length of 30 min, based on a recent Cochrane review including 69 RCTs, according to which longer interventions on alcohol had no benefit, the median duration being 25 min.[47] SI will also provide educational information about the nature of alcoholic AP and the risk of recurrence to the patients. Feasibility and cost-effectiveness were also considered.

Intervention in REAPPEAR-T

The repeated intervention will be provided by the same specially trained personnel and structured similarly to the SI. Each session will have the same structure but can be tailored to the patient's needs to strengthen motivation. Sessions will consist of three parts. First, the negative effects of alcohol and smoking on the pancreas will be highlighted. Second, the patient's motivation for abstinence and smoking cessation will be discussed. Third, the individual's responsibility in achieving the goals set after motivation assessment, with personalised advice.[13] We wish to enhance the efficacy of the repeated intervention by providing feedback for the patient based on the mean corpuscular volume and gamma glutamyl-transferase (GGT) values measured at the day of the interview.[48] The trained personnel providing the interventions will not take part in patient care in any form. A detailed protocol will be provided on request.

Concomitant care

Patients participating in cessation programmes or psychotherapy at the time of enrolment will not be eligible. Patients using self-help programmes and nicotine replacement therapy with commonly available products will not be excluded. The provided interventions encourage patients to seek help and try different strategies for alcohol and smoking cessation.

Outcomes

Primary endpoint

The primary endpoint of the REAPPEAR Study will be the composite of 2-year recurrence rate of AP irrespective of aetiology and 2-year all-cause mortality.

Secondary endpoints

1. ARP irrespective of aetiology (given as cumulative incidence and as rate of event) within 6, 12, 18 and 24 months.
2. Recurrence of alcohol-induced AP (rate of event) within 2 years.
3. The condition of 'likely pancreatitis' (fulfilling the diagnostic criteria of epigastric pain, a serum amylase or lipase level at least two times the upper normal level, and elevated leucocyte count or CRP levels, defined by Pelli *et al*.[49]
4. Length of hospital stay given in days (specifically due to recurrent pancreatitis and cumulative during follow-up).
5. Presentation to the emergency unit with and without hospital readmission (cumulative incidence).
6. Change of alcohol consumption and tobacco use (compared with baseline), estimated separately form biomarker levels and patient-reported consumption
7. CP (incidence within 2 years).[44]
8. Changes in body mass index (BMI) and blood pressure (compared with baseline).
9. Healthcare cost from the perspective of the health insurance fund within 2 years and quality-adjusted life-years (QALY).

Recruitment

Consecutively, all patients under treatment for alcohol-induced AP who received the SI according to standard protocol will be screened for eligibility, all eligible patients will be offered to participate in the REAPPEAR study. The potential benefits of participation will be highlighted to facilitate patient recruitment. The planned start and end dates of patient recruitment are 1 March 2021 and 1 December 2024.

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Biologic sample collection and biomarker measurements

At enrolment and every visit, basic laboratory tests from blood will be carried out and participants will provide blood, hair and urine samples for storage in the biobank.

Laboratory parameters measured are shown in online supplemental file 3. Laboratory results will be evaluated by a physician, who will decide whether further medical attention is necessary. All patients will receive the results of their laboratory tests in written form.

The samples in the biobank will be stored at −80°C and identified by the personal identification number (PIN) given at study entry. Planned alcohol and smoking biomarker measurements include urine and serum ethyl-glucuronide (or ethyl-sulfate) and hair nicotine measurements.[50 51] All samples will be collected and sent together to the laboratory when the patient number reached the preset goal for analysis. The results of the biomarker measurements will not be made accessible for patients. These measurements are only available in specialised laboratories, therefore, can be changed later due to feasibility issues.

Trial organisation, committees and boards

The corresponding centre of the REAPPEAR study is the Centre for Translational Medicine, Medical School, University of Pécs (www.tm-centre.org), whereas the coordinator and designer research team is the Hungarian Pancreatic Study Group (HPSG, https://tm-centre.org/en/study-groups/hungarian-pancreatic-study-group/). HPSG has been running high-quality international, multicentre clinical trials since 2014[41 52–54] and has published relevant guidelines for pancreatic diseases to improve patient care in pancreatology.[55 56]

The steering committee (SC) will be led by PH (principal investigator, specialist in internal medicine, gastroenterology and clinical pharmacology). SC members will be KO (study coordinator), a patient representative, NF (biostatistician), IH (psychologist) and the centre leaders. The SC will supervise the trial primarily and will make decisions regarding all critical questions overseeing patient safety, the progress of the trial, adherence to protocol, considering new information relevant to the trial and ensuring dissemination and implementation of the results.

All data gathered for research purposes will be handled confidentially and anonymously, which will be ensured by the data monitoring committee (DMC). Six-monthly audits are planned in each centre with continuous monitoring of the electronic case report forms (eCRFs) (online supplemental file 3) For each participant, a PIN will be generated and it will be present on all forms and documents of each individual.

The International Advisory Board will include Ole Petersen, Enrique de-Madaria and Jonas Rosendahl, providing independent external advice and guidance on strategic matters.

The study was designed by the SC and was supported by the University of Pécs Medical School. The sponsor had no role in the design of the trial and will have no access to the randomisation codes or the data. The sponsor will not participate in data monitoring, analysis and publication of results.

The independent safety monitor will be LC, who will ensure the safety of the patients and revise all reported harms possibly related to the intervention.

Data handling

Investigators will be responsible for the accuracy, reliability and quality of the collected data. Detailed data flow will be described in a data management plan. Data from completed eCRFs will be validated under the direction of the data manager on the DMC according to the data cleaning plan. Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form and will be documented for each subject before clean file status is declared. All changes to eCRFs will be recorded.

The DMC will perform an independent assessment of trial-related documents and activities to ensure respect for subjects' rights, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will also be checked.

After written consent of the subjects, data will be recorded by the investigators. Clinical research data will be processed separately from participants' personal data. Data may only be accessed by a person acting under the authority of the controller and in accordance with the authorisation system established within the controller's organisational structure, only to the extent and in the manner necessary for the performance of tasks. Personal data will not be made accessible to third parties. We will fully comply with the General Data Protection Regulation (GDPR).

Safety

Based on the nature of the combined brief intervention in REAPPEAR-T, we do not expect serious adverse events. However, minor or moderate adverse events may occur. Participants will be provided with information on alcohol and nicotine withdrawal alongside with the available options of professional help for addiction treatment. In case a potentially serious health problem is detected by the investigators related to the intervention, the safety monitoring board will be notified. The REAPPEAR-C is an observational study, hence adverse events are not applicable.

Randomisation and allocation concealment in REAPPEAR-T

Central randomisation will be performed with randomly permuted block size (2–6) and allocation ratio of 1:1 using a computer-generated random sequence. Inclusion and exclusion criteria will be rechecked prior to computer-aided randomisation via an online platform. The platform generates the PIN and a follow-up plan (with appointment dates). The randomisation procedure will be performed by the same person who screened and

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consented the patient. This person must be a doctor not actively participating in the treatment of the participant.

Blinding in REAPPEAR-T

Outcome assessors will be blinded to allocation. The medical personnel involved in the check-ups and treatment during a potential hospital re-admission will not be aware of the allocation. Since the nature of the intervention, the patient and the study nurse cannot be properly blinded.

Statistical analysis

Sample size calculation for REAPPEAR-T was based on the only published interventional randomised study assessing the effects of repeated brief interventions in alcohol-induced ARP, counting with a 2-year recurrence rate of 21.3% and an absolute reduction to 8.5%.[13 15 17 25] Considering one interim analysis on efficacy (with the Pocock correction), 80% power, 5% alpha (superiority design, two-sided) and a drop-out rate of 30%, the estimated sample size is 182 subject per study arm. This sample size calculation is expected to overestimate the minimum number of participants for three reasons: (1) the use of a combined intervention on alcohol and smoking and more frequent visits are expected to result in greater reduction of recurrence, (2) the use of a composite primary endpoint may result in higher event numbers and (3) the recurrence rate of AP is expected to be higher in the heavy-drinking smoker population, than in a mixed sample. The calculation was performed by Stata (V.15).

Safety analysis will be carried out on reaching 10% of the target patient enrolment, and a single interim analysis for efficacy and sample size re-estimation taking into consideration the observed drop-out rate at 50% of the expected total events of the primary outcome, which is 21. Early stopping will be executed (1) if safety concerns arise during the interim analysis or anytime later (stopping for safety concerns), (2) if the statistical power reaches at least 80% and $p<0.05$ for the primary outcome at the interim analysis (stopping for benefit), (3) if the results of the interim analysis show equal effects in both groups (stopping for futility) and (4) if power does not reach 80%, sample size will be re-estimated using the observed event and drop-out rate. In case the newly calculated sample size is unfeasible for the trial, both groups will continue follow-up according to the schedule of REAPPEAR-C (stopping for feasibility).

In the final analysis, intention-to-treat will be favoured over per-protocol (or 'as-treated') analysis. Information on mortality and hospitalisations will be obtained from the organisation responsible for handling data.

The 'last observation carried forward' strategy will be followed to impute missing data for other outcomes measured during the study.

Sample size calculation for the REAPPEAR-C will be carried out at the final analysis of the REAPPEAR-T, using available data from participants. Further enrolment will be performed according to the estimated sample size. These additional participants will receive the more effective or in case of equality the less costly intervention for alcohol and smoking cessation as determined by the results of the REAPPEAR-T. Participants of the cohort will be categorised into four groups primarily, according to smoking and drinking status (quit smoking; quit drinking; quit both; still smokes and drinks). Time of smoking and alcohol cessation will be taken into consideration. Participants who started smoking or drinking again after an abstinent period will be excluded from analysis in the REAPPEAR-C.

In descriptive statistics, the count and percentage will be provided for each treatment arm for binary outcomes. For continuous outcomes, number (n), mean, median, IQR (Q3–Q1), SD, minimum and maximum values will be provided for each treatment arm. In the univariate comparative analysis, we will calculate relative risk with 95% CI when comparing the primary endpoint between two groups (alpha=5%) with a reference arm using the control group complemented with χ^2 or Fisher's exact test (the same strategy will be followed for binary secondary outcomes). For continuous variables, we will use t-test assuming unequal variances or the Mann-Whitney test. We will perform univariate (Kaplan-Meier and Cox regression) and multivariate (Cox regression) survival analyses for binary outcomes. An adjustment will be carried out at least for age, sex, socioeconomic status, the number of prior ARPs, comorbidities, history of alcohol consumption (cumulative) and smoking (package year), severity and complications of index AP, BMI, cholecystectomy and enrolling centre. Mixed effect logistic regression will be conducted to estimate the effect of the multicomponent intervention on the outcomes, where the subject PINs will be used as a random subject. The model will be adjusted for changes in smoking habits, alcohol consumption, BMI, socioeconomic status, blood pressure and Maddrey score.[57]

All analyses will be carried out with SPSS V.26 and Stata V.15.

Drop-outs

Information on the primary outcome will be obtained either from the patient's documentation or from the National Health Insurance Fund or similar organisation managing data on healthcare costs and mortality, therefore information on the primary outcome will be available for most patients regardless of attendance of the study visits. Only withdrawal of consent will result in missing data.

Considering per-protocol analysis, in the REAPPEAR-T trial, missing more than one consecutive interventions after the initial assessment or withdrawal of consent during follow-up will result in the drop-out of the patient. In the REAPPEAR-C investigation, patients who withdraw consent during follow-up or miss the 2-year visit will be considered drop-outs, since data on current alcohol

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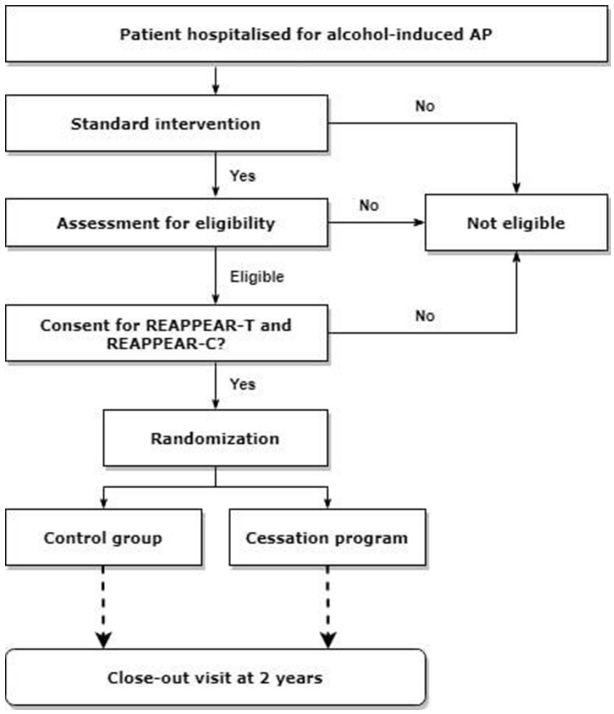

Figure 1 SPIRIT flow chart. Standard intervention will be provided for every patient as part of standard therapy. All randomised participants will be included in the REAPPEAR-T (trial) and REAPPEAR-C (cohort) as well. After reaching the required patient numbers for the REAPPEAR-T, further patients will be enrolled to the REAPPEAR-C in accordance with the estimated sample size. AP, acute pancreatitis. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials, REAPPEAR, Recurrent acute pancreatitis prevention by the elimination of alcohol and cigarette smoking.

consumption and smoking can only be obtained from the patient.

Flow and timing

Patients who met the inclusion criteria and none of the exclusion criteria will be offered to participate in the REAPPER-T trial. The enrolment period lasts from 48 hours before, until 1 week after hospital discharge. After informed consent and randomisation, participants will be assigned to the cessation programme or the control group (see at figure 1). All patients will appear at the clinic according to the study schedule (figure 2), within ±14 days from the prescheduled date.

We chose 3-monthly visits in the cessation programme based on a Swedish cohort study, in which 3-monthly brief interventions for selected patients with increased GGT levels were introduced and GGT levels were used for feedback. These interventions were found to reduce mortality, hospitalisation and sick leave significantly.[48] Hopefully, frequent visits will help in upholding motivation and improve adherence. Patients in the control group will have two prescheduled appointments, at 12 and 24 months.

	STUDY PERIOD	Screening enrollment period	Allocation	Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6		Visit 7		Close-out
			day 0	3 months		6 months		9 months		12 months		15 months		18 months		21 months		24 months
	GROUP	Both	Both	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	CG	CP	Both
ENROLLMENT	Eligibility screen	X																
ENROLLMENT	Standard intervention	X																
ENROLLMENT	Informed consent	X																
ENROLLMENT	Allocation		X															
	INTERVENTION				X		X		X		X		X		X		X	
ASSESSMENT	BP, HR, BMI		X		X		X		X	X	X		X		X		X	X
ASSESSMENT	Laboratory testing		X		X		X		X	X	X		X		X		X	X
ASSESSMENT	Questionnaires		X		X		X		X	X	X		X		X		X	X
ASSESSMENT	Sample collection		X		X		X		X	X	X		X		X		X	X

Figure 2 SPIRIT time table. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; BMI, body mass index; BP, blood pressure; CG; control group, CP; cessation programme, HR; heart rate.

Assessment

For the assessment of addiction and motivation to quit will be assessed by internationally recognised and validated questionnaires (online supplemental file 3).[58–64] This will enable the person who provides the intervention to individualise it and motivate the subject. Data on coffee consumption will be collected as well, as caffeine might counter the effects of alcohol in AP.[65] For the assessment of QoL, the EQ-5D-5L questionnaire will be used at baseline and every visit.[66 67] Socioeconomic status will be assessed at baseline and at 12 and 24 months with the questionnaire used in the LIFESPAN study.[68]

The aetiology of each recurrent episode will be determined following current international guidelines, but all episodes will be included in the primary endpoint.[4 34]

Blood pressure, heart rate and body weight will be measured by an independent nurse blind to the allocation at every visit. BMI will be calculated.

Cost-effectiveness

Cost-effectiveness analysis will be performed to examine the impact of the cessation programme on QoL, survival and health expenditure compared with the controls. We calculate the incremental cost-effectiveness ratio (ICER), which is defined by the difference in cost between the compared interventions (cessation programme with 3-monthly visits vs usual care), divided by the difference in their effect (QALY). The ICER will be evaluated based on the Hungarian cost-effectiveness threshold. The total cost of treatment per each individual will be obtained from the national database at the completion of the study.

Patient and public involvement

Five randomly selected patients from the HPSG database were invited. All of them had previous AP and would have been eligible for the study. Three patients attended the joint consultation. The original aims, hypotheses and protocol of the study were fully introduced to them. Patients insights were as follows: (1) they welcomed the study with great pleasure and felt it is highly important, (2) they found the primary endpoint fundamental, (3) they found the questionnaires and information sheets understandable, (4) they highlighted the importance of frequent visits to the clinic, and found the duration of the visits feasible, (5) they pointed out the necessity of

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high quality training of personnel providing the interventions, (6) they had absolutely no disapproval or negative feelings regarding regular blood tests, (7) they had no ethical objection concerning the control group and (8) they expressed high difficulties considering smoking cessation and favoured a step-down approach rather than immediate quitting.

We have revised and modified the original protocol accordingly.

DISCUSSION

Although alcohol and smoking are individual risk factors for AP, ARP and CP, they can synergise each other's effects.[69] In addition, there is a lack of evidence as to the means of preventive measures that could be used in everyday clinical practice concerning alcohol and tobacco use for AP patients. Also, the effect of smoking cessation on recurrence in drinkers and non-drinkers is not yet clear.

The REAPPEAR study aims to fill these gaps and provide specialists and primary care physicians with valuable information on the importance of alcohol and smoking cessation in AP and ARP. Furthermore, the feasibility, efficacy and cost-effectiveness of an intervention programme will be tested in this population to provide basis for large-scale intervention in alcohol-induced pancreatitis.

ETHICS AND DISSEMINATION

The REAPPEAR study is open for participation. Results of the planned analyses will be presented at national and international conferences and in peer-reviewed journals. Additional long-term follow-up of the participants is planned within the confines of the REAPPEAR+study.

The trial has been registered at the clinicaltrials.gov (NCT04647097). Amendments will be published under this registration number.

The Scientific and Research Ethics Committee of the Hungarian Medical Research Council approved the study (40394-10/2020/EÜIG). All local ethical approvals are in place. The study will be performed in accordance with the declaration of Helsinki, the principles of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and local legal and regulatory requirements.

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Society	Publication year	Title	Alcohol	Smoking or tobacco
AGA	2018	American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis	In patients with acute alcoholic pancreatitis, the AGA recommends brief alcohol intervention during admission (strong recommendation, moderate quality evidence)	-
IAP/APA	2013	IAP/APA evidence-based guidelines for the management of acute pancreatitis	Remarks: as treatment and follow-up depend on the etiology of pancreatitis (e.g. cholecystectomy for biliary pancreatitis **and dedicated follow-up visits after alcoholic pancreatitis to prevent recurrence** transabdominal ultrasonography should be performed on admission.	-
NICE	2018	Pancreatitis: summary of NICE guidance	Advise people with: – Pancreatitis caused by alcohol to stop drinking alcohol – Recurrent acute or chronic pancreatitis that is not alcohol related that alcohol might exacerbate their pancreatitis [Based on the experience and opinion of the GC]	Chronic pancreatitis to stop smoking in line with NICE's guidance on stop smoking interventions and services. [Based on the experience and opinion of the GC]

JPN	2015	Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points	-	-

Table S1. Guidelines on alcohol-induced AP

Supplementary material nr. 1

Tartalom

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Study structure

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World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04647097
Date of registration in primary registry	30 November, 2020
Last refreshed on	22 March 2021
Secondary identifying numbers	-
Source(s) of monetary or material support	European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020
Primary sponsor	University of Pécs
Secondary sponsor(s)	-
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Public title	Preventing the Recurrence of Acute Pancreatitis by Alcohol and Smoking Cessation (REAPPEAR)
Scientific title	Recurrent Acute Pancreatitis Prevention by the Elimination of Alcohol and Cigarette Smoking (REAPPEAR): Protocol of a Randomized Controlled Trial and a Cohort Study
Countries of recruitment	Hungary, Italy, Romania, Ukraine
Health condition(s) or problem(s) studied	Acute pancreatitis, alcoholic Recurrent acute pancreatitis
Intervention(s)	Standard intervention only Standard intervention (SI) will be a part of standard care in all participating centers, and will be provided for all acute pancreatitis patients, who are hospitalized and their condition is alcohol induced. A specially trained study nurse will deliver the intervention, since they were found to be the most effective regarding the decrease in alcohol consumption and smoking. The cost- effectiveness of the intervention and the feasibility were also taken into account. The Assist-linked brief intervention according to the World Health Organization (WHO) will serve as the base for the intervention, with an avarage of 30 minutes, based on a review containing 69 randomized controlled trials, which concluded that longer intervention do not have additional benefit. The patients will be also educated about the disease course of acute pancreatitis during the standard intervention.
	Standard intervention plus repeated intervention Standard intervention (SI) will be performed as described above. The repeated intervention will be delivered by the former mentioned same nurse and will be structured similarly to the standard intervention. Every visit and intervention will be individually altered according to the motivation of the patient, but they will follow the same structure. The sessions can be divided into three main parts: first, highlighting the harmful effects of smoking and alcohol on the pancreatic functions. Secondly, a discussion about the motivation of the patient will happen. The last portion of the session will focus on the responsibility of the individual to reach the desired goal will be highlighted. To enhance the efficacy of our intervention we wish

	to provide feed-back for the patient based on laboratory testing: the mean corpuscular volume (MCV) and gamma glutamyl-transferase (GGT) values will be measured right before the interview. The study nurse will not take part in patient care.
Key inclusion and exclusion criteria	Ages eligible for study: 18-65 years Sexes eligible for study: both Accepts healthy volunteers: no
	Inclusion criteria: -Patient hospitalized with alcohol-induced AP (defined by the revised Atlanta criteria) -Regular consumption of at least 40g (women)/ 50g (men) alcohol daily or 280g (women)/ 350g (men) alcohol during the preceding week of onset of abdominal pain -Every day smoker with at least 1-year history of smoking -Aged 18-65 years -Completed the standard intervention -Provided written informed consent
	Exclusion criteria: -Other possible etiologies for AP (eg. gallstones, hypertriglyceridemia above 11.5 mM , hypercalcemia, viral infection) and cases with more than one identified etiological factors -Major psychiatric illnesses (schizophrenia, bipolar disorder, dementia) -Currently receiving therapy for alcohol use disorder -Currently taking part in a smoking cessation program - 3 or more lifetime episodes of AP or diagnosed chronic pancreatitis -Undergoing active or palliative treatment for malignancy -Pregnancy -Life expectancy is less than two years
Study type	Allocation: Randomized Intervention Model: Parallel Assignment
	Intervention Model Description: Randomized controlled trial and a cohort study
	Masking: Single (Outcomes Assessor)
	Primary purpose: prevention
Date of first enrolment	-
Target sample size	364
Recruitment status	Not yet recruiting
Primary outcome(s)	Composite endpoint [Time Frame: 24 months] Recurrence rate of AP irrespective of etiology and all cause mortality
Key secondary outcomes	Recurrence of acute pancreatitis irrespective of etiology [Time Frame: 6, 18,24 months] Recurrence of acute pancreatitis irrespective of etiology given as cumulative incidence and as rate of event Recurrence of alcohol-induced AP [Time Frame: 24 months] Recurrence of alcohol-induced AP given as rate of event Likely pancreatitis [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months]

	Likely pancreatitis, fulfilling the diagnostic criteria of epigastric pain, a serum amylase or lipase level at least two times the upper normal level, and elevated leukocyte count or CRP levels Length of hospital stay [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Length of hospital stay given in days due to recurrent pancreatitis and overall during follow-up Presentation to the emergency unit, hospital re-admission [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Presentation to the emergency unit, hospital re-admission given as cumulative incidence Development of chronic pancreatitis [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Development of chronic pancreatitis given as incidence within 2 years Healthcare cost [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Healthcare cost from the perspective of the health insurance fund within 2 years Quality adjusted life years [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Quality adjusted life years (QALY) within 2 year Change of alcohol consumption given in gram per week [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Change of alcohol consumption compared to baseline given in gram per week based on patient reported data Change of tobacco use given in pieces per day [Time Frame: 3, 6, 9, 12, 15, 18, 21, 24 months] Change of tobacco use compared to the baseline given in pieces per day based on patient reported data

Requirements for centers

At least 60 patients admitted with AP yearly to the center

Minimum 12 patients (6/ group) enrolled

The standard intervention protocol for alcoholic AP patients must be implemented

Local ethical approval

Storage space for biological samples

Personnel:

1 study coordinator (responsible for participant selection, informed consent, schedule)

1 person providing the intervention

1 administrative personnel (data collection and upload, sample collection and storage)

Authorship policy

Centers can name two co-authors who actively particiapte in the organisation and coordination of patient enrollment.

Data Statement

Participant level data sharing is not planned.

Data Management Plan (DMP)

Collected data: Variables specified in Supplementary material 3 will be collected.

Data collection and handling: After informed consent, patients' data will be collected by clinical research administrators and uploaded to an electronic case report form (eCRF) in the Electronic Case Data Management System (ECDMS) run by the Institute for Translational Medicine, University of Pécs. All centers will access this platform by individual user accounts after receiving training. For each participant, a personal identification number (PIN) will be generated, and it will be present on all forms and documents of each individual. The list containing the PIN numbers and personal data of participants can only be accessed by the primary investigator after login by their protected personal account into the ECDMS.

Data validation: All data registered on the eCRFs will be validated first by local medical personnel, then the chief CRA and after by the study coordinator or chief investigator. Missing data will be requested from centers and improbable values will be double checked to elevate data quality.

Data use for others: Only study coordinators and the chief investigator will be able to access data from multiple centers.

Data preparation for transformations, preservation and sharing: Upon request, selected cases or data collected in a given time frame will be exported to a protected Excel sheet for analysis, containing the selected or all collected variables. If requested, other data formats, including comma-separated-values (CSV), Excel, SAS, R, and SPSS can be transformed.

Meta-data documentation: All data-related activities will be documented within the system and can be accessed by the coordinators and chief investigator.

Data repository: Long-term data storage will be managed within the ECDMS.

INFORMED CONSENT FORM

Recurrent Acute Pancreatitis Prevention by the Elimination of Alcohol and Cigarette Smoking

PERSONAL DETAILS:

First name:.....

Last name:.....

Date of Birth:.....

Insurance number:.....

Center:

Doctor:

PIN:

SUMMARY:

Dear Patient!

This Informed Consent Form is for men and women who attend the First Department of Internal Medicine, University of Pécs and who we are inviting to participate in a clinical trial regarding an alcohol and smoking cessation program in acute pancreatitis. The title of our research project is „Recurrent Acute Pancreatitis Prevention by the Elimination of Alcohol and Cigarette Smoking – REAPPEAR"

The pricinple investigatior is Prof. Peter Hegyi and the principal coordinator is dr. Klementina Ocskay. The coordinating center of the REAPPEAR study is the Institute for Translational Medicine, Medical Schoo, Universit of Pécs. Center costs (IT, biostatistics, trial organization etc.) are covered by the University of Pécs Medical School. This project is supported by „GINOP-2.3.2-15-2016-00048 - STAY ALIVE" co-financed by the European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020, and by Human Resources Development Operational Programme Grant EFOP 3.6.2-16-2017-00006 – LIVE LONGER which is co-financed by the European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020 as well as the Translational Medicine Foundation. The sponsor was not involved in the design of the study and will have no access to the database or the randomisation code.

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

Your doctor is involved in a research project at the First Department of Internal Medicine, University of Pécs. **Please read thoroughly the following information** and, if you agree, we ask you to undergo the below detailed intervention to support our research efforts. In case you do not want to participate in the research, we respect your decision of course and your decision will not result in any penalty, loss of benefits or change of treatment. Please feel free to consult any member of our team with your question or uncertainties.

Purpose of the research

Acute pancreatitis is the most common gastrointestinal disorder requiring hospitalisation, and almost one third of patients have recurrent episodes. The two most common causes are biliary duct obstruction and harmful alcohol consumption. There is no specific treatment, but there are ways to prevent these epsiodes by eliminating the causes. Our research focuses on alcohol consumption and smoking, which is an independent risk factor of acute pancreatitis. We would like tot test a specifically designed patient education and cessation program, which provides brief interventions to help patients quit or minimize alcoholc consumption and smoking.

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Principal coordinator: Klementina Ocskay Tel: +36 30 6235713 e-mail: ocskay.klementina@gmail.com
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INFORMED CONSENT FORM

Recurrent Acute Pancreatitis Prevention by the Elimination of Alcohol and Cigarette Smoking

Type of Research Intervention

This research will involve a brief intervention program, which will be provided by a specially trained personnel. You will visit the clinic according to a schedule, fill out some questionnaires, a nurse will measure your body weight, blood pressure and pulse. You will be asked to give blood, urine and hair samples.

Participant selection

We are inviting all adults aged 18-65 years with alcoholic acute pancreatitis who attend the First Department of Internal Medicine, University of Pécs to participate in the research on the patient education and cessation program.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will be offered the treatment that is routinely offered in this clinic/hospital for acute pancreatitis, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and protocol

Because we do not know if the patient education and cessation program is better than a one-time brief intervention on alcohol and smoking to prevent the recurrence of acute pancreatitis, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin.

Participants in one group will be taking part in the program while participants in the other group will receive the one-time brief intervention before they are discharged from the clinic. Participants in the program will visit the clinic eight times, while the other praticipants only to times. All participants will be asked to donate blood, urine and hair samples and to fill out questionaires. This way we can monitor your motivation and consumption. We will then compare which of the two has the best results.

We will take blood from your arm using a syringe and needle. Each time we will take about 40 ml blood, 30 ml of urine in a container and 30g hair. We will collect hair from the back of your scalp, being very careful so it will not show. At the end of the research all samples will be destroyed.

The healthcare workers will be looking after you and the other participants very carefully during the study. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

During the research you make eight or two visist to the clinic, depending on which group you were selected into.

- At every visit, you will be asked to fill out some questionnaires about why and home much your smoke and drink and how well your are feeling. A nurse will measure your body weight, blood pressure and pulse. You will be asked to give blood, urine and hair samples. Each time we will take about 40 ml blood, 30 ml of urine in a container and 30g hair. We will collect hair from the back of your scalp, being very careful so it will not show.
- If your were selected into the cessation program, a sepcially trained personel will sit down with you in private and you will talk about 30-60 minutes about your disorder and how you can prevent the recurrence of acute pancreatitis by quitting alcohol and smoking. They will try to help you find the best approach and achievening your goal.

Duration

The research takes place over two years in total. During that time it will be necessary for you to come to the clinic 2 or 8 days, depending on which group your are in. The final check-up will take place at two years, after that the research will be finished.

Side Effects

The cessation program in itself is safe and there are no expected side effectes. However, smoking and alcohol cessation can cause witdrawal symptoms, such as shaking and sweating. However, we will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. If this is necessary we will discuss it together with you and you will always be consulted before we move to the next step.

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Risks

By participating in this research it is possible that you will be at greater risk than you would otherwise be. There is, for example, a risk that your disease will not get better and cessation progrgam doesn't work as well as the one-time brief intervention, or that you will experience withdrawal.

While the possibility of this happening is very low, you should still be aware of the possibility. We will try to decrease the chances of this event occurring, but if something unexpected happens, we will provide you with special medication.

Benefits

You will recieve the results of your blood tests at every visist, free of charge. If anything alarming is seen, you will be immediately referred to a specialist.

Reembruisements

You will not be given any money or gifts to take part in this research.

Confidentiality

With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except Peter Hegyi, the principal investigator and Klementina Ocskay, the principal coordinator.

Sharing the Results

We will publish the results in order that other interested people may learn from our research. Confidential information will not be shared.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital. People who have alcoholic acute pancreatitis have a one-time brief intervention.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: Peter Hegyi, Tel: +36 70 375 1031 e-mail: hegyi2009@gmail.com or Klementina Ocskay Tel: +36 30 6235713 e-mail: ocskay.klementina@gmail.com.

This proposal has been reviewed and approved by the Scientific and Research Ethics Committee of the Hungarian Medical Research Council which is a committee whose task it is to make sure that research participants are protected from harm. Ethical approval number: 40394-10/2020/EÜIG. If you wish to find about more about the ethical approval or data protection, you can contact Dr. Szőke Gergely László, e-mail: adatvedelem@pte.hu, Tel.: (72) 501 599 / 23321 and Dr. Románcz Erzsébet, e-amil: romancz.erzsebet@pte.hu, Tel.: (72) 533 133 / 33018 .

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

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Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

At the time of signing I received a copy of the consent form and summary information.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness*_____** ***AND ***Thumb print of participant***

***Signature of witness* _____**

Date _____
Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1. the patient will participate in the REAPPEAR study, which is a randomized controlled clinical trial
2. patient data and biological samples will be collected and handled confidentially
3. the participant will be followed for two years
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____
Day/month/year

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Supplementary material nr. 3

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Randomization form

Name:

Social security number:

Date of birth:

Date of randomization:

Please tick in which applies from the following:

Inclusion criteria:

- Patient hospitalized with alcohol-induced AP
- Regular consumption of 4 (women)/ 5 (men) or more standard drinks right before the onset of abdominal pain
- Every day smoker (an adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day; CDC definition), with at least 1-year history of smoking
- individuals between 18-65 years of age [38]
- completed the standard intervention
- provided written informed consent

Exclusion criteria

- Other possible etiologies for AP (eg. gallstones, hypertriglyceridemia above 11.5 mM [39-41], hypercalcemia, viral infection) and cases with more than one identified etiological factors will be excluded
- Major psychiatric illnesses (schizophrenia, bipolar disorder, dementia)
- currently receiving therapy for alcohol use disorder
- currently taking part in a smoking cessation program
- at least 3 documented episodes of AP [42] or diagnosed chronic pancreatitis [43]
- undergoing active or palliative treatment for malignancy
- pregnancy
- life expectancy is less than two years

PIN number: (automatic)

Group: Cessation program / Control group (automatic)

Follow-up dates: (automatic)

FORM A – ENROLLMENT

1. Personal data

Date:.....

Social security number:……..

Name:……

Date of birth:……

Sex: Male/ Female

Race: White / Black / Indian / Asian / other: .....

Postal Code:.....

Phone Number:.....

Doctor providing information on the study:
Name:
Signature:
Doctor performing randomization:
Name:
Signature:
Person providing standard information:
Name:
Signature:
Date if informed consent:
Date of standard information:

2. Personal and medical history

Smoking:

Used tobacco product: conventional cigarette/ heated tobacco product (e.g. IQOS)/ e-cigarette/ other (pipe, chewing tobacco, dip, cigar):……
amount (cigarette / day): ……
How long (years)? ……

Alcohol consumption:
frequency: occasionally/monthly/weekly/daily
amount (g/day):……
since when? (years):……..
cumulative alcohol consumption in the last 2 weeks: ……..

Guide for estimation of the amount:
1 dl beer (4.5 vol. %) = ~3.5 g alcohol

1 dl wine (12.5 vol. %) = ~10 g alcohol
1 dl hard drink (50 vol. %) = ~40 g alcohol

Coffee consumption:
frequency: occasionally/monthly/weekly/daily
amount (espresso(s)/day):……
since when? (years):……
cumulative coffee consumption in the last 2 weeks (espressos): ……..

Drug abuse: yes / no (*Prescribed medication should not be included here.)*
if yes: type of drug:……
amount:……
for how many years:……

Pancreas disorders in family history: yes / no / no data (multiple choice)

acute pancreatitis: yes / no if yes: relationship to patient: .....
chronic pancreatitis yes / no if yes: relationship to patient: .....
autoimmune pancreatitis: yes / no if yes: relationship to patient: .....
pancreas tumor: yes / no if yes: relationship to patient: .....
other (please describe):……relationship to patient: .....

Co-morbidities

Diabetes mellitus: yes / no / no data
if yes: **Type?** Type I / Type II / Type III. / MODY / no data
Date of diagnosis (years)?.....

Hypertension: yes / no / no data
if yes: **Date of diagnosis (years)?**.....
(choose yes, if the patient has medication for it - even if blood pressure is in the physiological range)

COPD: yes / no / no data
if yes: **Date of diagnosis (years)?** .....

Asthma: yes / no / no data
if yes: **Date of diagnosis (years)?**.....

Other chronic respiratory disease: yes / no / no data
if yes: ..... **Date of diagnosis (years)?**..... …… ...
(emphysema, silicosis, chronic bronchitis, pulmonary fibrosis, sarcoidosis, in case of any doubt ask the physician)

Autoimmune disease: yes / no / no data
if yes: ..... . **Date of diagnosis (years)?**.....
(inflammatory bowel disease, SLE, rheumatoid arthritis, Sjögren's syndrome, Basedow's disease, Hashimoto's thyroiditis, scleroderma, Reiter's syndrome, multiple sclerosis, anemia perniciosa, celiac disease, autoimmune hepatitis, PBC, PSC, ITP, in case of any doubt ask the physician)

Cardiovascular diseases: yes / no / no data
if yes: **type**: IHD / STEMI / NSTEMI / infarction/ angina / heart failure /cardiomyopathy / peripheral vascular disease / other: ....
Since when (date: year)? .....
if heart failure: **NYHA class**: I / II / III / IV.
(IHD: ischemic heart disease, STEMI and NSTEMI AMI, ie subtypes of acute myocardial infarction; infarction: if data about ST-elevation is not available cardiomyopathy: DCM, ie dilatative, HCM i.e. hypertrophic, RCM i.e. restrictive peripheral vascular disease: generalized atherosclerosis, bypass, stent if heart failure develops as a consequence of any of these disease, please indicate it here separately)

Cirrhosis of the liver: yes / no / no data
if yes: **Date of diagnosis (years)?** .....
Child class: A / B / C

Other chronic liver disease: yes / no / no data
if yes, please specify ....
Date of diagnosis (years)? ..... ……..
(autoimmune hepatitis, PBC, PSC, adenoma, NAFLD, fatty liver, peilosis hepatis, intrahepatic cholestasis, chronic viral hepatitis, in case of any doubt the issue should be decided with medical help)

Dialysis-dependent: yes / no / no data
if yes: **Since when (date: year)?** ... ...

Other chronic kidney disease: yes / no / no data
if yes, please **specify:**..... .....
Date of diagnosis (years)? .....…
(decrease of eGFR may help; nephrosclerosis, cirrhosis of the kidney, renal artery stenosis, if the patient has only one kidney but it is working well then it should not be marked. In case of any doubt the issue should be resolved with medical help)

Medications

name of medication:……..……..
active substance:……
dose: ……. (number only!)
unit: g / mg / IU
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).……
how many times per day (e.g. 3): …….
method of administration: intravenous / oral /rectal/ subcutan /transdermal /inhalative
other notes: ……

3. Laboratory tests

Full blood count:
Red blood cell count (RBC)
Hemoglobin (HGB)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)

Platelet count (PLT)
Red cell distribution width (RDW)
White blood cell count (WBC)
Reticulocyte ratio (relative to RBCs)

Differential blood count:
Neutrophil, segmented
Neutrophil, band form
Neutrophil, metamyelocyte (juvenile form)
Eosinophil count
Basophil count
Monocyte count
Lymphocyte count

Hemostatic parameters:
international normalized ratio (INR)
prothrombin time

Ions:
Sodium
Potassium
Calcium

Metabolites:
Total bilirubin (TBIL)
Direct reacting bilirubin (DBIL)
Glucose
Blood urea nitrogen (BUN)
Creatinine
Total cholesterol
HDL-cholesterol
LDL cholesterol
Triglycerides

Proteins:
Albumin
Total protein
C-reactive protein (CRP)

Enzymes:
alpha-amylase
lipase
alanin-aminotransferase (ALAT/GPT)
aspartate-aminotranspherase (ASAT/GOT)
phosphatase (ALP)
gamma-glutamyl-transpeptidase (GGT)
lactate dehydrogenase (LDH)

4. Pancreas (mandatory fields)

Previous acute pancreatitis (in history): Yes/ No

If yes:

How many acute episodes are in the patient's medical history (not counting the episode at enrollment)?: ……

Date of the first documented episode (year): ……..……..

How many times was the participant hospitalized due to acute pancreatitis in the last two years (except the episode at enrollment)? ……..

Documented complications (of previous episodes)? Yes / No

If yes: calcifications/ pseudocyst/ fibrotic changes/ walled-off necrosis/ abscess/ acute peripancreatic fluid collection/ acute necrotic fluid collection/ pancreatic necrosis/ peripancreatic fat necrosis

Characteristics of the current (at enrollment) episode:

Length of stay: ……(days) (mandatory field) (calendar days)

Severity: mild/ moderate/ severe (mandatory field)

Local complications: yes/ no (mandatory field)

If yes: peripancreatic fluid collection/, pancreatic necrosis/ abscess/ peripancreatic fat necrosis/ pseudocyst / walled-off necrosis

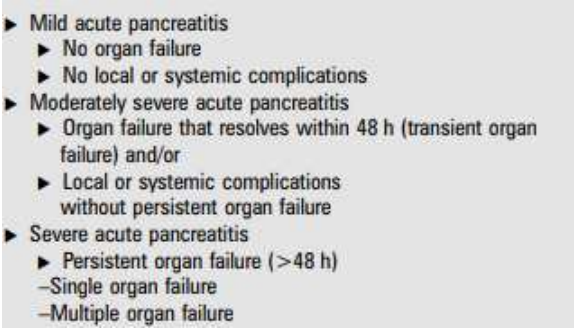
Systemic complications: yes/ no (mandatory field)

If yes: transient (less than 48 hours)/ persistent (at least 48 hours) (mandatory field)

Pancreatitis induced pleural fluid collection: (any day during hospitalization, mandatory field)

On-admission Marshall score (mandatory field)

Highest Marshall score during (current) hospitalization (mandatory field)



Local complications are peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected)

Table 1 Modified Marshall scoring system for organ dysfunction

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal*					
(serum creatinine, μmol/l)	≤134	134–169	170–310	311–439	>439
(serum creatinine, mg/dl)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mm Hg)†	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2
For non-ventilated patients, the FiO_2 can be estimated from below:					
Supplemental oxygen (l/min)	**FiO_2 (%)**				
Room air	21				
2	25				
4	30				
6–8	40				
9–10	50				

A score of 2 or more in any system defines the presence of organ failure.
*A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine ≥134 μmol/l or ≥1.4 mg/dl.
†Off inotropic support.

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"Closing" imaging: hypoechoic
Hypoechoic/ hyperechoic / peripancreatic fluid / irregular and blurred contours / Wirsung dilatation (above 1mm) / calcification / pseudocyst / inhomogeneous structure / fatty tissue infiltration / edematous pancreas / enlarged pancreas / hypodense / hyperdense / pancreatic necrosis / peripancreatic tissue necrosis / walled-off necrosis

Free abdominal fluid: yes / no

Pleural fluid: yes / no

Findings:

Hospital discharge report: file upload (anonym version only)

5. Biobank samples:

Type: serum/ plasma/ urine / hair

Date of sample collection:

Code:

FORM B – VISIT

1. Personal data

Date:.....

PIN:……...

Appeared at the visit: yes/ no
if no: cause: currently hospitalized/ died/ non-compliance / lost to follow-up / other: ……

2. Personal and medical history (since last visit)

Harmful substances

Smoking:

Used tobacco product: conventional cigarette/ heated tobacco product (e.g. IQOS)/ e-cigarette/ other (pipe, chewing tobacco, dip, cigar):……
amount (cigarette / day): ……
How long (month)? ……

Alcohol consumption:
frequency: occasionally/monthly/weekly/daily
amount (g/day):……
cumulative alcohol consumption in the last 2 weeks: ……..

Guide for estimation of the amount:
1 dl beer (4.5 vol. %) = ~3.5 g alcohol
1 dl wine (12.5 vol. %) = ~10 g alcohol
1 dl hard drink (50 vol. %) = ~40 g alcohol

Coffee consumption:
frequency: occasionally/monthly/weekly/daily
amount (espresso(s)/day):……
cumulative coffee consumption in the last 2 weeks (espressos): ……..

Drug abuse: yes / no (*Prescribed medication should not be included here.)*
if yes: type of drug:……

Co-morbidities DIAGNOSED SINCE ENROLLMENT

Diabetes mellitus: yes / no / no data
if yes: **Type?** Type I / Type II / Type III. / MODY / no data
Date of diagnosis (years)?.....

Hypertension: yes / no / no data
if yes: **Date of diagnosis (years)?**.....

(choose yes, if the patient has medication for it - even if blood pressure is in the physiological range)

COPD: yes / no / no data
if yes: **Date of diagnosis (years)?** .....

Asthma: yes / no / no data
if yes: **Date of diagnosis (years)?**.....

Other chronic respiratory disease: yes / no / no data
if yes: ..... **Date of diagnosis (years)?**..... …… ...
(emphysema, silicosis, chronic bronchitis, pulmonary fibrosis, sarcoidosis, in case of any doubt ask the physician)

Autoimmune disease: yes / no / no data
if yes: ..... . **Date of diagnosis (years)?**.....
(inflammatory bowel disease, SLE, rheumatoid arthritis, Sjögren's syndrome, Basedow's disease, Hashimoto's thyroiditis, scleroderma, Reiter's syndrome, multiple sclerosis, anemia perniciosa, celiac disease, autoimmune hepatitis, PBC, PSC, ITP, in case of any doubt ask the physician)

Cardiovascular diseases: yes / no / no data
if yes: **type**: IHD / STEMI / NSTEMI / infarction/ angina / heart failure /cardiomyopathy / peripheral vascular disease / other: ....
Since when (date: year)? .....
if heart failure: **NYHA class**: I / II / III / IV.
(IHD: ischemic heart disease, STEMI and NSTEMI AMI, ie subtypes of acute myocardial infarction; infarction: if data about ST-elevation is not available cardiomyopathy: DCM, ie dilatative, HCM i.e. hypertrophic, RCM i.e. restrictive peripheral vascular disease: generalized atherosclerosis, bypass, stent if heart failure develops as a consequence of any of these disease, please indicate it here separately)

Cirrhosis of the liver: yes / no / no data
if yes: **Date of diagnosis (years)?** .....
Child class: A / B / C

Other chronic liver disease: yes / no / no data
if yes, please specify ....
Date of diagnosis (years)? ..... …….....
(autoimmune hepatitis, PBC, PSC, adenoma, NAFLD, fatty liver, peilosis hepatis, intrahepatic cholestasis, chronic viral hepatitis, in case of any doubt the issue should be decided with medical help)

Dialysis-dependent: yes / no / no data
if yes: **Since when (date: year)?** ... ...

Other chronic kidney disease: yes / no / no data
if yes, please **specify:**..... .....
Date of diagnosis (years)? .....…
(decrease of eGFR may help; nephrosclerosis, cirrhosis of the kidney, renal artery stenosis, if the patient has only one kidney but it is working well then it should not be marked. In case of any doubt the issue should be resolved with medical help)

Medications

name of medication:……..……..
active substance:……
dose: ……. (number only!)
unit: g / mg / IU
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).……
how many times per day (e.g. 3): …….
method of administration: intravenous / oral /rectal/ subcutan /transdermal /inhalative
other notes: ……

3. Laboratory tests

Full blood count:
Red blood cell count (RBC)
Hemoglobin (HGB)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count (PLT)
Red cell distribution width (RDW)
White blood cell count (WBC)
Reticulocyte ratio (relative to RBCs)

Differential blood count:
Neutrophil, segmented
Neutrophil, band form
Neutrophil, metamyelocyte (juvenile form)
Eosinophil count
Basophil count
Monocyte count
Lymphocyte count

Hemostatic parameters:
international normalized ratio (INR)
prothrombin time

Ions:
Sodium
Potassium
Calcium

Metabolites:
Total bilirubin (TBIL)
Direct reacting bilirubin (DBIL)
Glucose
Blood urea nitrogen (BUN)

Creatinine
Total cholesterol
HDL-cholesterol
LDL cholesterol
Triglycerides

Proteins:
Albumin
Total protein
C-reactive protein (CRP)

Enzymes:
alpha-amylase
lipase
alanin-aminotransferase (ALAT/GPT)
aspartate-aminotranspherase (ASAT/GOT)
phosphatase (ALP)
gamma-glutamyl-transpeptidase (GGT)
lactate dehydrogenase (LDH)

4. Quit-smoking products and strategies

Nicotine replacement therapy (patch, inhaler, gum, lozenge, spray, strip etc.): yes/ no
Bupropion: yes/ no
Varenicline: yes/no
Exercise program: yes/no
Applications/websites: yes/no
Self-help program/ methods: yes/no
Help from a specialist: yes/no
Other: ……..

5. Alcohol quitting strategies

Pharmacotherapy (disulfiram, GHB, naltrexone, nalmefene etc.): yes/ no
Treatment by addictologist: yes/ no
Psychotherapy: yes/ no
Self-help program/methods: yes/ no
Alcoholics Anonymous or similar groups: yes/ no
Institutional rehabilitation/ detoxification: yes/ no
Other: ……

6. Admission SINCE ENROLLMENT/LAST FOLLOW-UP

Presentation at the emergency room: yes/no
if yes:
date:
cause: alcohol-related/ non-alcohol related
diagnosis: pancreatitis / other: ……
Admission: yes/no
if yes:

date:
cause: alcohol-related/ non-alcohol related
diagnosis: pancreatitis / other: …….
Length of stay: (days)

7. Biobank samples

Type: serum/ plasma/ urine / hair

Date of sample collection:

Code:

SOCIOECONOMIC STATUS

1. Education

What is the highest grade or level of school you have completed or the highest degree you have received?

Never attended / Kindergarten only / 1st Grade / 2nd Grade / 3rd Grade / 4th Grade / 5th Grade / 6th Grade / 7th Grade / 8th Grade / 9th Grade / 10th Grade / 11th Grade / 12th Grade, no diploma / High school graduate/ Ged or equivalent / Some college, no degree / Associate degree: occupational, technical, or vocational program / Associate degree: academic program / Bachelor's Degree (example: Ba, Ab, Bs, Bba) / Master's Degree (example: Ma, Ms, Meng, Med, Mba) / Professional School Degree (example: Md, Dds, Dvm, Jd) / Doctoral Degree (Example: Phd, Edd) / Refused / Don't Know

How many years have you spent at school or in full time study? _____

2. Occupation

What is your current occupation? ……..

What is your current employment status?

Employed for wages (full time work) / Employed for wages (part time work) / Self-employed

Out of work and looking for work → since / Out of work but not currently looking for work →

since:…….. / A housewife / A student / Military / Retired → since:…….. / Unable to work → since:……..

Please characterize your job:

Heavy physical labor Yes/ No

If yes: Do you perceive it as a health threat? Yes/No

Noise, dust, gases, vapors, "polluted" air Yes/ No

If yes: Do you perceive it as a health threat? Yes/No

Work stress (time pressure, concentration), worry about job security Yes/ No

If yes: Do you perceive it as a health threat? Yes/No

Overtime, long working hours Yes/ No

If yes: Do you perceive it as a health threat? Yes/No

Shift work/night shift Yes/ No

If yes: Shift work without night shift/ Shift work with night shift / Always night shift

Do you perceive it as a health threat? Yes/No

How long have you been doing that work? …… years month

3. Income

Monthly average income (net, €):

Less than 150 € / 150 € to 300 € / 300 € to 1000 € / 1000 € to 3500 € / 3500 € to 7500 € / over 7500 €

/ No data

4. Subjective Social Status

Where would you place yourself on this ladder?

Please **place a large "X"** on the rung where you think you stand at this time in your life, relative to other people in your country.

File upload:

EQ-5D-5L

Mobility: I have no problems in walking about / I have slight problems in walking about / I have moderate problems in walking about / I have severe problems in walking about /I am unable to walk about

Self-care: I have no problems washing or dressing myself / I have slight problems washing or dressing myself / I have moderate problems washing or dressing myself / I have severe problems washing or dressing myself /I am unable to wash or dress myself

Usual activities (e.g. work, study, housework, family or leisure acitivites): I have no problems doing my usual activities/ I have slight problems doing my usual activities / I have moderate problems doing my usual activities /I have severe problems doing my usual activities / I am unable to do my usual activities

Pain/ discomfort: I have no pain or discomfort / I have slight pain or discomfort / I have moderate pain or discomfort / I have severe pain or discomfort / I have extreme pain or discomfort

Anxiety/ depression: I am not anxious or depressed / I am slightly anxious or depressed /I am moderately anxious or depressed /I am severely anxious or depressed /I am extremely anxious or depressed

Your health today:

File upload:

AUDIT

1. How often do you have a drink containing alcohol?

Never (0 points)
Monthly or less (1 point)
2 to 4 times a month (2 points)
2 to 3 times a week (3 points)
4 or more times a week (4 points)

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

1 or 2 (0 points)
3 or 4 (1 point)
5 or 6 (2 points)
7, 8, or 9 (3 points)
10 or more (4 points)

3. How often do you have six or more drinks on one occasion?

Never (0 points)
Less than monthly (1 point)
Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

4. How often during the last year have you found that you were not able to stop drinking once you had started?

Never (0 points)
Less than monthly (1 point)
Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

Never (0 points)
Less than monthly (1 point)
Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

Never (0 points)
Less than monthly (1 point)
Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

Never (0 points)
Less than monthly (1 point)

Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

Never (0 points)
Less than monthly (1 point)
Monthly (2 points)
Weekly (3 points)
Daily or almost daily (4 points)

9. Have you or someone else been injured as a result of your drinking?

No (0 points)

Yes, but not in the last year (2 points)

Yes, during the last year (4 points)

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

No (0 points)

Yes, but not in the last year (2 points)

Yes, during the last year (4 points)

Score: (automatic)

Revised drinking motives questionnaire

Do you drink? Yes/ no

If yes:

How often do you drink……

1. To forget your worries.
2. Because your friends pressure you to drink.
3. **Because it helps you enjoy a party.**
4. **Because it helps you when you feel depressed or nervous.**
5. To be sociable.
6. **To cheer up when you are in a bad mood.**
7. Because you like the feeling.
8. So that others won't kid you about not drinking
9. Because it's exciting.
10. **To get high.**
11. **Because it makes social gatherings more fun.**
12. **To fit in with a group you like.**
13. **Because it gives you a pleasant feeling.**
14. **Because it improves parties and celebrations.**
15. Because you feel more self-confident and sure of yourself.
16. To celebrate a special occasion with friends.
17. **To forget about your problems.**
18. **Because it's fun.**
19. **To be liked.**
20. **So you won't feel left out.**

Scoring for every question:
Almost Never/Never (1 point)
Some of the time (2 points)
Half of the time (3 points)
Most of the time (4 points)
Almost Always/Always (5 points)

DMQ-R original (automatic)
Social score:
Coping score:
Enhancement score:
Conformity score:

DMQ-R short form (automatic)
Social score:
Coping score:
Enhancement score:
Conformity score:

Fagerstrom Nicotine Dependence Test

Do you currently smoke cigarettes?

Yes / No

If "yes," read each question below. For each question, enter the answer choice which best describes your response.

1. How soon after you wake up do you smoke your first cigarette?
   Within 5 minutes (3 points)
   6 to 30 minutes (2 points)
   31 to 60 minutes (1 points)
   after 60 minutes (0 points)

2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema)?
   No (0 points)
   Yes (1 point)

3. Which cigarette would you hate most to give up?
   The first one in the morning (1 point)
   Any other (0 point)

4. How many cigarettes per day do you smoke?
   10 or less (0 points)
   11 to 20 (1 point)
   21 to 30 (2 points)
   30 or more (3 points)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   No (0 points)
   Yes (1 point)

6. Do you smoke when you are so ill that you are in bed most of the day?
   No (0 points)
   Yes (1 point)

Comments:

Score: (automatic)

Motivation for quitting smoking:

Are you planning to quit smoking?

Yes, within the next month /Yes, within the next 6 months /Yes, beyond 6 months /No, not at all /I don't know

If yes, …….:

How much do you want to quit?

a little/ somewhat /a lot