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## High versus low energy administration in the early phase of acute pancreatitis (GOULASH): A multicentre randomized double-blind clinical trial

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## High versus low energy administration in the early phase of acute pancreatitis

### (GOULASH trial): A multicentre randomized double-blind clinical trial

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3 Word count: 4286  
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7 **ABSTRACT**  
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11 **Introduction.** Acute pancreatitis (AP) is an inflammatory disease with no specific therapy  
12 Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently  
13 discovered early event in the pathogenesis. Importantly, preclinical research showed that  
14 intracellular ATP delivery restores the physiological function of the cells and protects from  
15 cell injury suggesting that restoration of energy levels in the pancreas is therapeutically  
16 beneficial. Despite several, high quality and experimental observations in this area, no  
17 randomized trials have been conducted to date to address the requirements for energy intake  
18 in the early phase of AP.  
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21  
22 **Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial.  
23 Patients suffering from AP will be randomly assigned to groups A (30kcal/kg/day energy  
24 administration starting within 24h of hospital admission) or B (no energy administration in  
25 the first 24h of hospital admission). Energy will be delivered with nasoenteric tube feeding  
26 with additional intravenous glucose supplementation or total parenteral nutrition if necessary.  
27 A combination of multi organ failure for more than 48h and mortality is defined as primary  
28 endpoint, whereas several secondary endpoints such as length of hospitalization or pain will  
29 be determined to elucidate more detailed differences between the groups. The general  
30 feasibility, safety and quality checks required for high quality evidence will be adhered to.  
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34 **Discussion.** This study will provide evidence whether early high-energy nutritional support is  
35 beneficial in the clinical management of AP.  
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39 **Trial registration:** The trial has been registered at the ISRCTN (ISRCTN 63827758).  
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3 **Keywords:** acute pancreatitis, energy administration, enteral feeding, randomised clinical  
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## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets have been identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors: bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters, a common mechanism is mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1, 9]. In experimental pancreatitis models the same observations have been revealed [10-21]. Although these experimental observations clearly suggest that restoration of energy level could be a therapeutic tool in AP, this has not been translated into clinical trials.

One of the best and most physiological way of delivering energy to a patient is enteral nutrition (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering from severe AP showed that mortality is 27% with EN, versus 57% without EN [34]. Importantly EN not only decrease mortality, but also reduces the frequency of multi-organ failure and the necessity of interventions in patients suffering from severe AP (SAP) [35]. No data are available on whether early or on demand nutrition/energy

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3 supply is beneficial in SAP. The recently published Dutch PYTHON study suggests that there  
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5 is no difference on early versus on demand enteral tube feeding in SAP but patients may have  
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7 received insufficient amount of energy at the early phase of the disease [36, 37]. In the early  
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9 EN group patients received over 20 kcal/kg/day only from the third day onwards whereas in  
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11 the on demand group they received energy supplementation only from the day six [37]. In  
12  
13 mild and moderate AP (MAP) much less information is available concerning the usefulness of  
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15 EN. There is a large variety of protocols on EN in MAP. Immediate oral feeding [38],  
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17 nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used. Notably  
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19 immediate oral feeding significantly decreased the length of hospital stay (LOH) [38]. Early  
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21 (within 24h) nasogastric EN was not only well tolerated but reduced the intensity and duration  
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23 of abdominal pain decreased the necessity for opiates and almost completely eliminated the  
24  
25 risk of oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early  
26  
27 EN in MAP and SAP we performed a systematic review and meta-analysis which showed that  
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29 early EN can be beneficial in both, MAP and SAP [35]. However, we also realized the lack of  
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31 multicentre randomized control trials addressing energy intake in the early phase of AP.  
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36 The main objective of this trial is to understand whether early energy supplementation to  
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38 patients suffering from acute pancreatitis is beneficial.  
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## 42 **METHODS**

### 43 **1. Design**

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45 This is a randomised controlled two-arms double-blind multicentre trial. Patients suffering  
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47 from acute pancreatitis will be randomly assigned to groups A (high energy administration  
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49 starting within 24h of hospital admission) and B (low energy administration after 24h of  
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51 hospital admission).  
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## 2. Trial organization, committees and boards

GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

International translational advisory board (ITAB): The committee will include gastroenterologist (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the progress of the study and will give advice to the SC.

The study was designed by SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation Office. Neither sponsors was involved in the design of the study, and they will have no access for the database management or to the randomisation code.

### 3. Study population

All patients diagnosed with AP will be informed on the possibility of taking part in the GOULASH study. After the consent form is signed, patients will be randomized by a computer using a block randomisation protocol. Figure 1 shows the flow chart of participants according to CONSORT2010 guideline [53].

**Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the “2 out of 3” criteria of the IAP/APA guideline [52]: (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3) written informed consent form is signed.

**Exclusion criteria:** (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6) already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.

**Sample size:** Sample size calculation was based on the National Hungarian Registry operated by the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF (multi organ failure) existing more than 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10% drop-out rate, 80% power and 95% significance level. The calculation was performed by the Independent data-management and biostatistics provider company (IDMB, Adware Research LTD, Balatonfüred, Hungary).

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3 **Randomisation:** In each centre participants will be divided in 2 groups receiving one of the  
4 two study treatments. The allocation of participants to the different groups will be carried out  
5 based on predefined randomisation lists created separately for each recruiting centre. The  
6 randomisation lists will be prepared with a block size of 4 and with an allocation ratio of 1:1.  
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#### 13 14 **4. Duration**

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16 The planned starting date of the study is: 1 January, 2017, and the planned finishing date of  
17 the study is: 1 January, 2020  
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#### 23 **5. Blinding**

24 The medical staff (e.g., taking the measurements such as blood pressure, examining health  
25 records for events such as abdominal pain, reviewing and interpreting examination results  
26 such as X-ray or CT) and the patient receiving the intervention will be blinded to knowledge  
27 of treatment assignment. The person providing the intervention cannot be blinded in this  
28 study.  
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#### 38 **6. Intervention**

39 Based on the currently available guidelines enteral feeding can be started at any time for the  
40 patients suffering from AP. In addition no calorie restriction/order has been described.  
41 Therefore both groups can be regarded as being treated within accepted practice  
42 recommendations.  
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49 In this study, early high energy administration will be the intervention. Patients will be  
50 randomised to group A or B: see flowchart.  
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3 **Groups:** In **group A**, high energy will be delivered after admission. Patients will receive a 10  
4 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will immediately  
5 started as follows: On Day 0 (from admission until the start of EN (can be vary from 2-24 h)):  
6 calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day  
7 will be provided until the oral feeding starts. In **group B**, low energy administration after  
8 hospital admission. Patients will receive a NG or NJ feeding tube at admission as described  
9 above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day.  
10 On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30  
11 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A  
12 and B only the amount of calories administered will be different. Patients will receive the  
13 same amount of fluid and ions during EN (see below).  
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27 **Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

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29 **Energy:** 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate:** 18.3g (49%E), **Fat:** 5.8g  
30 (35%E) + **Minerals:** 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus,  
31 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil  
32 Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).  
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38 **Zero Energy Enteral Tube Feed (100ml):**

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40 **Energy:** 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate:** 0g, Fat: 0g + **Minerals:** 134mg Sodium,  
41 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride  
42 (0%E) (in this study the local institutional pharmacy will provide it in accordance with the  
43 Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture  
44 of the above mentioned two solution will be used.  
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51 **Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml  
52 will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250  
53 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In  
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3 case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ  
4 tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.  
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7 **Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for  
8 24 h and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing  
9 ones) orally plus enteral tube feed (440ml, 720 kcal/day) will be started on the day when: (1)  
10 abdominal pain has been ceased for at least 6 h before the new day started, (2) CRP level has  
11 started decreasing and are below 100 mg/L and (3) amylase or lipase level has started  
12 decreasing  
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20 **Start of total feeding** (around 2000 kcal): If the patients have no symptoms during the mixed  
21 oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding  
22 (according to local policy) can be started.  
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27 **Other issues:** The speed of EN will be different for the patients (depends on the body  
28 weight), however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties  
29 reaching the 30 kcal/kg/day calories intake (if the patients body weight is above 75 kg)  
30 additional intravenous calorie will be added using Sterofundin G. Maximum of 2000 ml (=   
31 400 kcal) can be delivered in this way. If NG feeding is not tolerated, NG tube will be  
32 replaced to NJ tube as described above. If NJ feeding is not tolerated, EN will be reduced by  
33 50% and increased again gradually until tolerated. If the re-increasing process is still not  
34 tolerated TPN will be started to reach the required energy target. In case of severe AP, TPN  
35 has to be delivered via central venous catheter.  
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## 50 **11. Other treatment of subjects**

51 General treatment indicated by the IAP/APA guideline will to be utilized [52].  
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## 56 **12. Discharge of patients**

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3 Uniformisation of length of hospital stay is necessary to avoid bias concerning LOH. Re-  
4 admission within one week after discharge has to be considered as the same hospital  
5 admission. Patients has to be counted as discharged from hospital/from the study when (1) the  
6 total feeding was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral  
7 feeding, (3) CRP level is less than 50 mg/L, (4) abdominal pain has completely resolved (5)  
8 no other pancreatitis-related complication requiring hospitalization is detected.  
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### 19 **13. Endpoints**

20 The following primary endpoints will be calculated: A combination of Multi Organ Failure  
21 more than 48h and Mortality. The following secondary endpoints will be analysed: (1)  
22 pancreatic necrosis, (2) nutrition related complications: diarrhoea, aspiration pneumonia,  
23 pneumothorax due to central TPN catheter placement, (3) need for conversion from NG to NJ  
24 feeding tube (4) need for conversion from EN to TPN, (5) days until the start of total feeding,  
25 (6) use of antibiotics, (7) pain relapse, (8) CRP, (9) WBC, (10) PCT, (11) infection, (12)  
26 length of hospital stay, (13) need for ICU admission, (14) length of ICU therapy, (15) organ  
27 failure, (16) complications, (17) costs calculation.  
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### 40 **14. Monitored parameters during hospitalization**

41 There will be a large variety of parameters monitored during the study (e.g. medical history,  
42 physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A  
43 will contain the parameters collected on admission. Form B will contain parameters collected  
44 every day during hospitalization. Form C will contain parameters collected 1 month after  
45 hospital discharge. For details see supplementary materials or web page  
46 (<http://www.pancreas.hu/en/studies/goulash>), which will be available from February 2017.  
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3 Data collection on the case report form (CRF) will be done electronically (see data  
4 management)  
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### 9 10 **15. Data management and statistical analyses**

11 **Data handling:** Data will be handled by IDMB. Electronic CRF will be used. The  
12 Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed  
13 data flow will be described in Data Management Plan (DMP). Data from completed eCRFs  
14 will be validated under the direction of the Data Manager at IDMB according to Data  
15 Cleaning Plan (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will  
16 be referred back to the Investigator using a data query form (DQF), and be documented for  
17 each individual subject before clean file status is declared. All changes to eCRF will be  
18 recorded. Before Data Base Lock Data Review Meeting will decide and document necessary  
19 steps related to any issue in the database and define the analysis sets. Member of the data  
20 review meeting are delegated investigator, biostatistician and data manager. AEs will be  
21 coded using MedDRA. AdWare Research Ltd., who will act as IDMB, works according to  
22 GCP, GLP, FDA 21CFR PART11 and other relevant regulatory requirements. AdWare Ltd.  
23 has GLP and ISO 9001 certificates.  
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### 43 **Study populations:**

44 Three analysis populations will be defined:

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47 Safety Analysis Set (SAS): all patients enrolled to the study.  
48  
49 Per Protocol Set (PPS): all enrolled patients who finished the study conforming  
50 to the requirements of the Study Protocol.  
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54 Intention to Treat (ITT) all randomised participants who start on a treatment,  
55 excluding consent withdrawals.  
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5 **Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit  
6 recommendation for dropouts from the PPS group with reasons given to SC. All  
7 recommendations will be filed. SC will discuss all the information and if the alteration in the  
8 protocol would be expected to have any bearing on the interventions and outcomes of the  
9 study, the patient will not be included in the final per-protocol analysis. Automatic dropout  
10 from the per-protocol group shall be ordered if: (1) any of the exclusion criteria diagnosed  
11 during the course of AP, (2) at least 50% of the energy requirement is not achieved on any  
12 days during the study, (3) parameters required for answering the primary endpoints are  
13 missing or (4) serious medical reasons not related to pancreatitis (i.e. accidents, stroke) occur.  
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27 **Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later)  
28 statistical packages; Microsoft MSWord will be used for reporting.  
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34 **Statistical Methods:** Baseline patient and disease characteristics will be analysed by using  
35 descriptive analysis. Demographic and baseline characteristics will be summarized for the  
36 overall study population. Continuous variables will be described by mean, median, standard  
37 deviation, and ranges and categorical variables will be described by absolute and relative  
38 frequencies. A graphical presentation of efficacy variables will be prepared, if applicable.  
39 Descriptive statistics for both of the primary and secondary parameters will be analysed  
40 similarly. Mean changes (and their 95% CI) from baseline to end-of-study visit will be  
41 presented as well. Chi-squared tests will be applied to compare proportions between the  
42 different groups. Mortality/extended M0F will be investigated using the Kaplan-Meier  
43 analysis method; while subgroup comparisons will be performed using the Chi-squared or  
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3 Fisher's exact test, as appropriate. For safety data, descriptive statistics and individual listings  
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5 of adverse events will be also presented.  
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10 **Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under  
11 40y, 40y-60y, 60y-80y), (2) BMI (below 20, 20-25, 25-30, 30-35, above 35), (3) the start of  
12 abdominal pain before admission ( $\leq 24h$ ,  $\leq 48h$ ,  $\geq 48h$ ), (4) severity of the disease SAP and  
13 MAP. All subgroup analyses, (5) etiologies will be done descriptively. No confirmatory  
14 statistical testing will be applied. Hence, statistical tests and the p-values attached to them will  
15 be regarded as descriptive and not as tests of hypotheses.  
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Details of the applied statistical tests will be described in the Statistical Analysis Plan.

#### 16. Early quality assessment.

Early quality assessment check will be performed after the first 100 patients. IDMB (AdWare Ltd.) 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. IDMB will report to SC. SC will discuss all the information and if the differences would be expected to have any bearing on the interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of all participants who were randomized or allocated into each group or the differential dropout rate is above 15 percent between the arms, the study needs to be reassessed and IDMB will make recommendations regarding either reevaluation of power calculation, extension of recruitment period, extension of number of study centers or termination of trial.

#### 17. Interim analyses and premature termination of the study.

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2  
3 IDMB can also recommend to stop the trial early for ethical reasons if one of the groups  
4  
5 clearly shows evidence of a significant benefit. An interim-analysis will be performed on the  
6  
7 primary endpoint when 50% of patients have been randomised and discharged from hospital.  
8

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10 The interim-analysis will be performed by the IDMB. IDMB will report to SC.

11  
12 The Haybittle–Peto boundary approach will be used. If interim analysis shows a probability of  
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14 equal to, or less than 0.001 that a difference as extreme between the treatments is found, given  
15  
16 that the null hypothesis is true, then the trial will be stopped early.  
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### 19 20 21 **18. Centres**

22  
23 The trial will start in two centres (University of Debrecen and University of Pécs), after which  
24  
25 the study is open for other centres. In all cases IDMB will make an audit of the centre and will  
26  
27 report to the SC. SC keeps the right to decide whether the centre meets the required quality to  
28  
29 join the study. Compulsory requirements for a centres: (1) it needs to treat at least 50 AP  
30  
31 patients a year, (2) it needs to have all the equipment required for the study, (3) besides the  
32  
33 regular medical team the centre has to appoint at least one doctor and one nurse/administrator  
34  
35 fully available for the trial with no additional commitments which can interfere with her/his  
36  
37 duty when her/his availability is required, (4) the blinding described above can be fully  
38  
39 utilized, (5) all persons need to attend a preliminary meeting where all the details concerning  
40  
41 the studies are discussed fully and have qualified as investigators in a GCP course. Centres  
42  
43 wish to join needs to send a letter of intent to the corresponding author by e-mail.  
44  
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### 49 50 **19. Publication policy**

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52 Centres providing more than 25 patients can provide two authors to the authorship list. Every  
53  
54 additional 25 patients will give the opportunity to nominate an additional author.  
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## 20. Feasibility

As a general protocol for the treatment of AP at the Centre for Translational Medicine at the University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the Emergency Department. Patients data between the period of 1 January – 31 May 2016 were analysed and the following observations were noted: (1) In 85% of all AP admission early EN could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients tolerated NG feeding without any complications. The rest of the patients who had gastric retention or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature data described in the introduction. Concerning the number of patients. At the University of Pécs around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore, if no other Institution would join the study it can be completed within 3 years.

## 21. Safety

Since no unknown drugs/therapy are used in the study no adverse and serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. In this trial IDMB will examine safety variables after every 16 patients have completed. Moreover, investigators will report AE or SAE via a separate form which has to be sent to IDMB and

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2  
3 SC. SC will discuss and if the adverse effect is confirmed it will be reported to the relevant  
4 institutional and national ethical committee <http://www.ett.hu/tukeb.htm>.  
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## 8 9 10 **22. Additional information and future plan.**

11 Blood samples (serum and plasma) will be stored from all patients in order to study laboratory  
12 parameters later if required (e.g. the laboratory could not measure it), and in order to build up  
13 a biobank for later clinical studies to which all participants will given informed consent. The  
14 samples will be stored on -80°C. A follow-up study (called GOULASH PLUS) is under  
15 preparation in order to follow the patients for up to 5 years after the study. The study protocol  
16 will also be published.  
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## 27 **DISCUSSION**

28 Here we report the protocol of a prospective double-blind RCT to study the effects of early  
29 energy restoration in AP. The pre-clinical studies [ 1, 9] and meta-analyses [35] suggest that  
30 energy supplementation should be beneficial. Our main hypothesis is that elevating the energy  
31 level of acinar and ductal cells will prevent these cells from injury, therefore, it will decrease  
32 the extent of necrosis during AP. Since both the local and systemic complications (immune  
33 response) are largely depend on the extent of the necrosis we propose that this intervention  
34 will reduce multi-organ failure and mortality in AP.  
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## 47 **CONCLUSION**

48 This study provides the first and type A evidence concerning the necessity of energy intake  
49 for patients suffering from AP.  
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## 55 **List of abbreviations**

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3 AP – acute pancreatitis

4  
5 CRP – C-reactive Protein

6  
7 DCP – data cleaning plan

8  
9 DMP – data management plan

10  
11 DQF – data query form

12  
13 eCRF – electronic clinical research form

14  
15 EN – enteral nutrition

16  
17 GOULASH – name of the study: general utilization of early energy administration in acute  
18  
19 pancreatitis.

20  
21 HPSG – Hungarian Pancreatic Study Group

22  
23 ICU – intensive care unit

24  
25 ITAB – International Translational Advisory Board

26  
27 LOH – length of hospital stay

28  
29 MAP – mild and moderate AP

30  
31 MOF – multi organ failure

32  
33 NG – nasogastric

34  
35 NJ – nasojejunal

36  
37 PCT – procalcitonin

38  
39 PN – parenteral nutrition

40  
41 PPS – Per Protocol Set

42  
43 SAS – Safety Analysis Set

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45 SAP – severe AP

46  
47 SC – Steering Committee

48  
49 TPN – total parenteral nutrition

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51 WBC – white blood cell count

**Declarations**

The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research Ethics Committee of the Medical Research Council.

**Availability of data and materials**

Not applicable, because the trial have not completed patient recruitment.

**Competing interest**

The authors declare that they have no competing interests.

**Funding**

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**Authors' contributions**

All authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study KM, ANS, DP and PV are going to randomize the patients and ensure the blinding. AM, KS, JB, SG, MP, PS, ZV and TT are going to manage the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will

1  
2  
3 prepare the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS  
4  
5 will be members of SC. PH and KM drafted the manuscript.  
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All adult patients with an episode of acute pancreatitis (AP)

- Exclusions
- Not meeting inclusion criteria
- (1) Patients above 18y
  - (2) diagnosed AP on the basis of the "2 out of 3" rule of IAP/APA guideline
  - (3) written informed consent form is signed
- Meeting exclusion criteria
- Hospitalization >72 hours before admission
  - Abdominal pain >120 hours (5 days)
  - Delirium tremens
  - Child-Pugh C stage liver cirrhosis
  - AP due to malignancy
  - Already on artificial nutrition (EN or PN)
  - Pregnancy
  - BMI above 40 or below 18
  - Age above 80
  - Ketoacidosis
  - CT with contrast is contraindicated

X patients to be randomised

X Assigned to start high energy enteral nutrition < 24 hours after randomisation

X Assigned to start low energy enteral nutrition < 24 hours after randomisation

X Analysed

X Analysed

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**FORM-A****Acute  
Pancreatitis****GOULASH**

**The physical examination has to be done ON ADMISSION!**  
**The blood for laboratory parameters has to be drawn ON ADMISSION!**  
**This form has to be filled ON ADMISSION!**

**Questionnaire****1. Patient personal details**

Insurance number:.....  
 First name:.....  
 Last name: .....,  
 Date of birth:.....  
 Gender: female male  
 Ethnicity/Race: White / Black / Asian-Indian Not known

**2. Details from the medical history**

**Alcohol consumption:** yes / no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/day):.....  
 since when? (years):.....  
 Alcohol consumption in the last 2 weeks: .....,  
 if not:  
 Did you drink alcohol earlier? yes/no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/occasion):.....  
 For how many years?.....  
 How long ago did you stop drinking alcohol?.....

*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

**Smoking:** yes / no  
 if yes: amount (cigarettes/day):.....  
 For how many years? .....,  
 if not:  
 Did you smoke earlier? yes/no  
 if yes: amount (pcs/occasion):.....  
 For how many years?.....  
 How long ago did you stop smoking? .....,

**Drug abuse:** yes / no *Prescribed medication should not be included here.*  
 if yes: type of drug:..... amount:.....  
 since when (year):.....  
 (if there are more drugs, please describe them in the NOTES section at the end)

**Diabetes mellitus:** yes / no  
 if yes: type: Type I. / Type II./Type III. c / MODY  
 since when (year):.....

Country:

Town:

Hospital:

Doctor:

Patient No:

THE RCT IS ORGANIZED BY THE HUNGARIAN PANCREATIC STUDY GROUP

FORM-A

Acute Pancreatitis

GOULASH

**Lipid metabolism disorder:** yes / no  
 if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no *Not counting the current episode.*  
 if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other  
 if other: please describe:.....

If the patient had ACUTE PANCREATITIS in the history:  
 How many times did the patient have acute episodes before this episode:.....  
 When did the patient have the first acute episode (year):.....

If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:  
 When was it diagnosed?.....  
 How many times did the patient have acute episodes before this episode:.....  
 When did the patient have the first acute episode (year):.....

If the patient has PANCREATIC CANCER::  
 When was it diagnosed?.....  
 Was the patient diagnosed with chronic pancreatitis? yes / no  
 If yes, when was it diagnosed?.....  
 How many times did the patient have acute episodes before this episode?:.....  
 When did the patient have the first acute episode (year):.....

Other information:  
 .....

**Pancreas disorders in family history:**  
 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:.....  
 .....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data  
 if yes: please describe:.....

**Other illnesses:** yes / no  
 if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*  
 if yes:  
 name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

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**FORM-A****Acute  
Pancreatitis****GOULASH**

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

**Diet:** yes / no  
if yes: please describe:.....

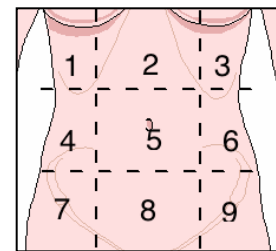
**3. Etiology** *The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to "Idiopathic" if etiological factor was not identified.*

Biliary	yes	no	no data
Alcohol	yes	no	no data
Virus infection	yes	no	no data
Trauma	yes	no	no data
Drug-induced	yes	no	no data
Congenital anatomical malformation	yes	no	no data
Cystic fibrosis	yes	no	no data
Gluten-sensitive enteropathy	yes	no	no data
Hypertriglyceridaemia	yes	no	no data
Genetic	yes	no	has not been tested yet
Idiopathic	yes	no	
Other	yes	no	

if yes: please describe:.....

**4. Complains, symptoms**

**Abdominal pain:** yes / no  
if yes: since when (hours):.....  
type: cramping / dull / sharp  
intensity (1-10):.....  
location: diffuse / localized  
Please mark the location!  
radiation:.....



**Nausea:** yes / no

**Vomiting:** yes / no  
if yes: how many times:.....  
contents of cast:.....

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# FORM-A

# Acute Pancreatitis

# GOULASH

**Subfebrility/fever:** yes / no

if yes: since when:.....  
degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no

if yes: how much (kg):.....  
How long did it take? (weeks):.....

**Jaundice:** yes / no

if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

*Please refer to the period just before your symptoms has started.*

## 5. Admission details and state

**Blood pressure (Hgmm):**.....

**Heart rate (/minute):**.....

**Body weight (kg):**.....

**Body height (cm):**.....

**Respiratory rate (/minute):**.....

**Body temperature (°C):** .....

axillary/rectal

**Oxygen saturation (%):** .....

Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no

**Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

**Glasgow Coma Scale:**

**Eye response**

- 4 points: Spontaneous eye opening
- 3 points: Eye opening in response any speech
- 2 points: Opening to response to pain
- 1 point: No eye opening

**Motor Response**

- 6 points: Obeying command
- 5 points: Localizing response to pain
- 4 points: Withdraws to pain
- 3 points: Decorticate posture
- 2 points: Decerebrate posture
- 1 point: No response to pain

**Verbal Response**

- 5 points: Orientated
- 4 points: Confused conversation
- 3 points: Inappropriate speech
- 2 points: Incomprehensible speech
- 1 point: No verbal response.

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**FORM-A****Acute  
Pancreatitis****GOULASH****6. Laboratory parameters on admission****OBLIGATORY PARAMETERS:**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
Serum glucose (mmol/l)	
Hemoglobin A1C (%)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
C-reactive protein (mg/l)	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	

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# Acute

# FORM-A

# Pancreatitis

# GOULASH

**OTHER PARAMETERS (if measured):**

IgA (g/l)	
IgM (g/l)	
IgG (g/l)	
IgG4 (g/l)	
CA 19-9 (U/ml)	
PaO <sub>2</sub> (Hgmm)	
HCO <sub>3</sub> (mmol/l)	
sO <sub>2</sub> (%)	
sweat chloride (mmol/l)	
urine amylase	
urine lipase	
urine creatinine	
(other)	

Virus serology: yes / no Which viruses? ..... results:.....

### 7. Imaging examinations on admission

Does the patient have pleural fluid? yes no N/A

Does the patient have lung infiltrate? yes no N/A

Does the patient have abnormal pancreatic structure? yes no N/A

If yes: hypoechoic/hyperechoic/peripancreatic fluid/irregular and blurred contours/Wirsung dilatation (above 1mm)/ascites/calcification/cyst

**Abdominal X-ray:** yes no  
Description:  
.....  
.....

**Chest X-ray:** yes no  
Description:  
.....  
.....

**Chest Computed Tomography:** yes no  
Description:  
.....  
.....

**Abdominal Computed Tomography:**  
Modified CTSI Score: .....0-10.....  
*Please NOTE! Abdominal CT is compulsory on admission*

**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

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**FORM-A****Acute  
Pancreatitis****GOULASH**- **CTSI:****I. Pancreas**

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**

- presence of extrapancreatic findings

**DETAILED REPORT**- **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 (nonenhancement):**

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60%, above 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

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# Acute

# Pancreatitis

# GOULASH

# FORM-A

**12. Epicrisis** *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
 .....

### NOTES

.....  
 .....

### DATE:

YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION:            HOUR ..... MIN: .....

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ..... **SIGNATURE:** .....

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ..... **SIGNATURE:** .....

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# FORM-B

# Acute Pancreatitis

# GOULASH

PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY

Day No:  
Date (+hour, min)

GOULASH No:  
(Automatically generated)

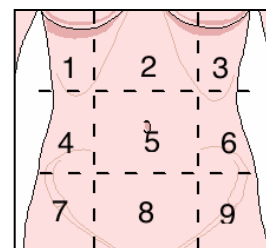
## 1. Patient personal details

First name:.....

Last name: .....

## 2. Complains, symptoms

**Abdominal pain:** yes / no  
if yes: since when (hours):.....  
type: cramping / dull / sharp  
intensity (1-10):.....  
location: diffuse / localized  
Please mark the location!  
radiation:.....



**Nausea:** yes / no  
*If YES, retention measurement has to be performed.*

**Vomiting:** yes / no  
*If YES, NG tube has to be replaced by NJ tube.*

**Subfebrility/fever:** yes / no  
if yes: since when:.....  
degree (°C):.....

**Appetite:** good / retained / bad

**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

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# FORM-B

# Acute Pancreatitis

# GOULASH

### 3. Patient's state

Blood pressure (Hgmm):..... Heart rate (/minute):.....

Body weight (kg):.....

Respiratory rate (/minute):.....

Body temperature (°C): .....  
axillary/rectal

Oxygen saturation (%): .....

O2 therapy: yes/no

Abdominal tenderness :       yes / no

Abdominal guarding:       yes / no

Jaundice:                       yes / no

Glasgow Coma Scale (GCS):.....

**Glasgow Coma Scale:**

**Eye response**

- 4 points: Spontaneous eye opening
- 3 points: Eye opening in response any speech
- 2 points: Opening to response to pain
- 1 point: No eye opening

**Motor Response**

- 6 points: Obeying command
- 5 points: Localizing response to pain
- 4 points: Withdraws to pain
- 3 points: Decorticate posture
- 2 points: Decerebrate posture
- 1 point: No response to pain

**Verbal Response**

- 5 points: Orientated
- 4 points: Confused conversation
- 3 points: Inappropriate speech
- 2 points: Incomprehensible speech
- 1 point: No verbal response.

### 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

## FORM-B

Acute  
Pancreatitis

## GOULASH

**OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	
IgA (g/l)	
IgM (g/l)	
IgG (g/l)	
IgG4 (g/l)	
CA 19-9 (U/ml)	
PaO <sub>2</sub> (Hgmm)	
HCO <sub>3</sub> (mmol/l)	
sO <sub>2</sub> (%)	
sweat chloride (mmol/l)	
urine amylase	
urine lipase	
urine creatinine	
(other)	

**Blood glucose (by finger stick test)** *Compulsory on the first day:*

4h	mmol/l	amount of insulin if administered : ..... IU
8h	mmol/l	
12h	mmol/l	
16h	mmol/l	
20h	mmol/l	
24h	mmol/l	

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# FORM-B

# Acute Pancreatitis

# GOULASH

**5. Imaging (if performed)**

yes no

**Abdominal ultrasonography:**

yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

**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:

.....  
 .....

**Abdominal X-ray:**

yes no

Description:

.....  
 .....

**Chest X-ray:**

yes no

Description:

.....  
 .....

**Chest Computed Tomography:**

yes no

Description:

.....  
 .....

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## FORM-B

Acute  
Pancreatitis

## GOULASH

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:

## I. Pancreas

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

## II. Size of Necrosis

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

## III. Extrapancreatic findings

- presence of extrapancreatic findings
- 

## DETAILED REPORT

## - 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 (nonenhancement):

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

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

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# Acute

# FORM-B

# Pancreatitis

# GOULASH

- Distant **abdominal fluid**:
  - o Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - o Moderate amount (easy to see, but without pelvic or abdominal distension)
  - o Large amount with abdominal/pelvic distension
  
- **Pleural effusion**:
  - o none
  - o one sided:..... (AP diameter: ..... cm)
  - o Both sides, L - ..... cm, R - ..... cm
  
- **Extrapancreatic findings**:
  - o Inflammation (Cholecystitis, Duodenitis, etc.) location: .....
  - o Cholecystolithiasis
  - o Choledocholithiasis
  - o Signs of bowel ischaemia
  - o Bowel distension, ileus
  - o Venous thrombosis
  - o Pseudoaneurysm
  - o Parenchymal organ involvement, define: .....

Other Description:

.....

.....

## 6. Microbiology examination

Biological sample collection                      yes                      no

If yes:                      place: /blood, urine, airway, pancreas, other/

result:                      .....

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# Acute

# FORM-B

# Pancreatitis

# GOULASH

**Pain management:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:**                    yes    no

if yes,

name of the medication:.....

dosage:.....

**Intensive care:**        yes    no

if yes,

namely (ventilation, vasopressor therapy):.....

**Other:**

if yes,

please describe:.....

.....

.....

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# FORM-B

# Acute Pancreatitis

# GOULASH

### 8. Interventions, endoscopic treatment:

yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage  
 Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent  
 Early complications: none/bleeding/perforation

ERCP: yes no

if yes:

Successful biliary cannulation: yes no if yes: notes: .....  
 Precut: yes no if yes: needleknife/precut papillotomy  
 EST: yes no if yes: biliary/pancreatic  
 Stone extraction: yes no  
 Stent: yes no if yes: metal/plastic  
 How many pcs? diameter(Fr)? length(cm)?  
 Pancreatic duct filling: yes no if yes: notes: .....

### 9. Complications

Pancreatic: yes no no data  
 if yes, fluid collections / pseudocyst / necrosis / diabetes  
 Organ failure: yes no  
 if yes, lung / heart / kidney /other  
 Duration of organ failure: <48 hours >48 hours  
 Death: yes no  
 if yes: the exact time of death: ..... e.g. 10.25 or 22.45

### NOTES

.....  
 .....  
 .....

### DATE:

YEAR: ..... MONTH: ..... DAY: .....

NAME OF THE DOCTOR: .....SIGNATURE: .....

NAME OF THE NURSE: .....SIGNATURE: .....

NAME OF THE SCIENCE ADMINISTRATOR: .....SIGNATURE: .....

THE RCT IS ORGANIZED BY THE HUNGARIAN PANCREATIC STUDY



**HPSG chair and leader of the Steering Committee:**  
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FORM-C

Acute Pancreatitis

GOULASH

Questionnaire

1. Patient personal details

First name:.....

Last name: .....

GOULASH No:

(Automatically generated)

2. Details from the medical history (in the last month)

Alcohol consumption: yes / no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/day):.....

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

Smoking: yes / no  
 if yes: amount (cigarettes/day):.....

Drug abuse: yes / no *Prescribed medication should not be included here.*  
 if yes: type of drug:..... amount:.....  
 (if there are more drugs, please describe them in the NOTES section at the end)

Any re-hospitalization?: yes / no  
 if yes: cholecystectomy: yes no  
 recurrent AP: yes no  
 other: .....

Medications taken regularly in the last month: yes / no  
*Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*  
 if yes:  
 name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

**FORM-C****Acute  
Pancreatitis****GOULASH****Diet:** yes / no

if yes: please describe:.....

**3. Complains, symptoms****Abdominal pain:** yes / no

if yes: since when (hours):.....

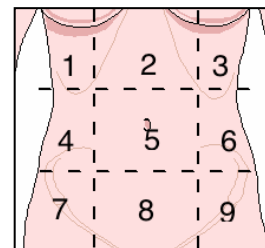
type: cramping / dull / sharp

intensity (1-10):.....

location: diffuse / localized

Please mark the location!

radiation:.....

**Nausea:** yes / no**Vomiting:** yes / no

if yes: how many times:.....

contents of cast:.....

**Subfebrility/fever:** yes / no

if yes: since when:.....

degree (°C):.....

**Appetite:** good / retained / bad**Weight loss:** yes / no

if yes: how much (kg):.....

How long did it take? (weeks):.....

**Jaundice:** yes / no

if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus**4. Laboratory parameters****OBLIGATORY PARAMETERS**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

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**OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	

**5. Imaging examination**

**Abdominal ultrasonography:**                      yes                      no

Description:

**Ultrasound:**

- **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)

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**FORM-C****Acute  
Pancreatitis****GOULASH**

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- Size of peripancreatic fluid or pseudocyst: ..... cm
  - **Pancreas homogeneity:**
    - o Homogenous
    - o Inhomogeneous, includes area(s) of low echogenicity
    - o Inhomogeneous, includes calcifications
  - In case of circumscribed low echogenicity area, it's size: ..... cm
  - **Wirsung** dilatation: YES / NO (yes, diameter: ..... mm)

21 Other Description:

22 .....  
23 .....  
24 .....  
25 .....

26  
27 **Abdominal Computed Tomography:** yes no  
28 Modified CTSI Score: .....0-10.....

29 *Please NOTE! Abdominal CT is compulsory if*

30 *- Abdominal ultrasonography is not fully completed OR*

31 *- There is any alteration on abdominal ultrasonography*

32  
33 **CTSI Score: (I)** Normal pancreas 0 point, intrinsic  
34 pancreatic abnormalities with or without inflammatory  
35 changes in peripancreatic fat 2 points, Pancreatic or  
36 peripancreatic fluid collection or peripancreatic fat  
37 necrosis 4 points **(II)** Necrosis absent 0 Points, < 30%  
38 necrosis 2 Points, > 30% necrosis 4 points **(III)** presence of  
39 extrapancreatic findings 2 points.  
40 MAXIMUM OF: 10 points

41 - **CTSI:**

42 **I. Pancreas**

- 43 o Normal pancreas  
44 o Intrinsic pancreatic abnormalities with or without inflammatory changes in  
45 peripancreatic fat  
46 o pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

47 **II. Size of Necrosis**

- 48 o Necrosis absent  
49 o < 30% necrosis  
50 o > 30% necrosis  
51 o > 60% necrosis

52 **III. Extrapancreatic findings**

- 53 o presence of extrapancreatic findings

54 **DETAILED REPORT**

55 - **Pancreas Size:**

- 56 o Normal  
57 o Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5  
58 cm, none exceeds 3 cm)

# Acute

# GOULASH

## FORM-C

## Pancreatitis

- 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** (nonenhancement):
  - Largest diameter of necrosis area: ..... cm
  - Location of necrosis: .....
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 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
  - Choledocholithiasis
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: .....

Other Description:

.....  
.....



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# FORM-C

# Acute Pancreatitis



**6. Complications** *Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:**                    yes                    no                    no data  
if yes:                    fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:**                yes                    no  
if yes:,                    lung /heart / kidney /other

**Death:**                        yes                    no  
If yes: the exact date of death: ..... e.g. 10.25 or 22.45

**7. Epicrisis** *A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
.....

**DATE:**  
YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

**NAME OF THE DOCTOR** : .....**SIGNATURE:** .....

For peer review only





## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3,4
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4, 7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	14, 11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	13-14
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	6-7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11-12
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	18
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	18, 7

1			
2		assessing outcomes) and how	
3			
4		11b If relevant, description of the similarity of interventions	7-8
5	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	12
6		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
7			
8	<b>Results</b>		
9	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
10	diagram is strongly	were analysed for the primary outcome	6-7
11	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
12	Recruitment	14a Dates defining the periods of recruitment and follow-up	7,16
13		14b Why the trial ended or was stopped	
14			
15	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
16	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
17		by original assigned groups	
18			
19	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
20	estimation	precision (such as 95% confidence interval)	
21		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
22	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
23		pre-specified from exploratory	
24			
25	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
26			
27	<b>Discussion</b>		
28	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
29	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
30	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
31			
32	<b>Other information</b>		
33	Registration	23 Registration number and name of trial registry	2,18, 1
34	Protocol	24 Where the full trial protocol can be accessed, if available	16
35	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18
36			

37

38 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also

39 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

40 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

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# BMJ Open

## High versus low energy administration in the early phase of acute pancreatitis (GOULASH): Protocol of a multicentre randomized double-blind clinical trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-015874.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Jun-2017
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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Medical management
Keywords:	Pancreatic disease < GASTROENTEROLOGY, Adult gastroenterology < GASTROENTEROLOGY, Gastroenterology < INTERNAL MEDICINE

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**High versus low energy administration in the early phase of acute pancreatitis (GOULASH  
trial): Protocol of a multicentre randomized double-blind clinical trial**

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Word count: 6548

**ABSTRACT**



1 **Introduction.** Acute pancreatitis (AP) is an inflammatory disease with no specific therapy.  
2  
3 Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently  
4  
5 discovered early event in the pathogenesis. Importantly, preclinical research showed that  
6  
7 intracellular ATP delivery restores the physiological function of the cells and protects from cell  
8  
9 injury suggesting that restoration of energy levels in the pancreas is therapeutically beneficial.  
10  
11 Despite several, high quality and experimental observations in this area, no randomized trials have  
12  
13 been conducted to date to address the requirements for energy intake in the early phase of AP.  
14  
15

16 **Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial. Patients  
17  
18 suffering from AP will be randomly assigned to groups A (30 kcal/kg/day energy administration  
19  
20 starting within 24h of hospital admission) or B (low energy administration during the first 72h of  
21  
22 hospital admission). Energy will be delivered with nasoenteric tube feeding with additional  
23  
24 intravenous glucose supplementation or total parenteral nutrition if necessary. A combination of  
25  
26 multi organ failure for more than 48h and mortality is defined as the primary endpoint, whereas  
27  
28 several secondary endpoints such as length of hospitalization or pain will be determined to elucidate  
29  
30 more detailed differences between the groups. The general feasibility, safety and quality checks  
31  
32 required for high quality evidence will be adhered to.  
33  
34  
35  
36

37 **Discussion.** This study will provide evidence whether early high-energy nutritional support is  
38  
39 beneficial in the clinical management of AP. The results of this trial will be published in an open  
40  
41 access way and disseminated among medical doctors.  
42  
43

44 **Ethical Approval:** The study has been approved by the relevant organization, The Scientific and  
45  
46 Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU).  
47

48 **Trial registration:** The trial has been registered at the ISRCTN (ISRCTN 63827758).  
49

50 **Keywords:** acute pancreatitis, energy administration, enteral feeding, randomized clinical trial  
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## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets were identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors the early phase of AP is almost the same. Bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters cause mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1, 9]. In experimental pancreatitis models the same observations have been revealed [10-21]. Although these experimental observations clearly suggest that restoration of energy level could be a therapeutic tool in AP, this has not been translated into clinical trials.

One of the best and most physiological way of delivering energy to a patient is enteral nutrition (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering from severe AP (SAP) showed that mortality is 27% with EN, versus 57% without EN [34]. Importantly EN not only decreases mortality but also reduces the frequency of multi-organ failure and the necessity of interventions in patients suffering from SAP [35]. No data are available on whether early or on demand nutrition/energy supply is beneficial in SAP. The recently published Dutch PYTHON study suggests that there is no difference on early versus on demand enteral tube

1 feeding in SAP but patients may have received an insufficient amount of energy at the early phase  
2 of the disease [36, 37]. In the early EN group patients received over 20 kcal/kg/day only from the  
3 third day onwards whereas in the on demand group they received energy supplementation only  
4 from day six[37]. In mild and moderate AP (MAP) much less information is available concerning  
5 the usefulness of EN. There are a large variety of protocols on EN in MAP. Immediate oral feeding  
6 [38], nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used. Notably  
7 immediate oral feeding significantly decreased the length of hospital stay (LOH) [38]. Early (within  
8 24h) nasogastric EN was not only well tolerated but reduced the intensity and duration of  
9 abdominal pain, decreased the necessity for opiates and almost completely eliminated the risk of  
10 oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early EN in MAP  
11 and SAP we performed a systematic review and meta-analysis which showed that early EN can be  
12 beneficial in both, MAP and SAP [35]. However, we also realized the lack of multicentre  
13 randomized control trials addressing energy intake in the early phase of AP.  
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15 The main objective of this trial is to understand whether early energy supplementation to patients  
16 suffering from AP is beneficial. Our hypothesis is that early energy supplementation will prevent  
17 the cells from death or decrease the size of necrosis if occur. This will decrease systemic immune  
18 response that will be ended in lower frequency of multi organ failure (MOF) and mortality. To  
19 prove this concept a randomized clinical trial involving all AP patients must be organized.  
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## 43 **METHODS**

### 44 **1. Design**

45 This is a randomized controlled two-arms double-blind multicentre trial. Patients suffering from  
46 acute pancreatitis will be randomly assigned to groups A (high energy administration starting within  
47 24h of hospital admission) and B (no energy administration after 24h of hospital admission).  
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### 56 **2. Trial organization, committees and boards**

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GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

International translational advisory board (ITAB): The committee will include gastroenterologist (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the progress of the study and will give advice to the SC.

The study was designed by SC and ITAB. The study is financially sponsored by the University of Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation Office. Neither sponsors were involved in the design of the study, and they will have no access to the database management or to the randomization code.

### 3. Study population

All patients diagnosed with AP will be informed of the possibility of taking part in the GOULASH study. After the consent form is signed, a computer using a block randomization protocol will

1 randomize the patients. Figure 1 shows the flow chart of participants according to SPIRIT 2013  
2 statement[52].  
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6 **Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the “2 out of 3”  
7 criteria of the IAP/APA guideline[53] : (a) upper abdominal pain; (b) serum amylase or lipase >3x  
8 upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those  
9 patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3)  
10 written informed consent form is signed.  
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17 **Exclusion criteria:** (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours  
18 (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6)  
19 already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age  
20 above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.  
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26 **Sample size:** Sample size calculation was based on the National Hungarian Registry operated by  
27 the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF existing more than  
28 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether  
29 they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of  
30 the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10%  
31 drop-out rate, 80% power and 95% significance level. The calculation was performed by the  
32 Independent data management and biostatistics provider company (IDMB, Adware Research LTD,  
33 Balatonfüred, Hungary).  
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44 **Randomization:** In each centre participants will be divided into 2 groups receiving one of the two  
45 study treatments. The allocation of participants to the different groups will be carried out based on  
46 predefined randomization lists created separately for each recruiting centre. The randomization lists  
47 will be prepared with a block size of 4 and with an allocation ratio of 1:1.  
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#### 53 54 55 4. Duration 56 57 58 59 60

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2 The planned starting date of the study is; 1 January 2017, and the planned finishing date of the  
3 study is; 1 January 2020.  
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## 8 **5. Blinding**

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10 The medical staff (e.g., taking the measurements such as blood pressure, examining health records  
11 for events such as abdominal pain, reviewing and interpreting examination results such as X-ray or  
12 CT) and the patient receiving the intervention will be blinded to knowledge of treatment  
13 assignment. The person providing the intervention cannot be blinded in this study. Sealed envelopes  
14 ensure the allocation sequence. Nutritional support equipment will be covered until the fourth day to  
15 ensure that only who made the randomization will know which group the patient was enrolled into.  
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## 23 **6. Intervention**

24 Based on the currently available guidelines enteral feeding can be started at any time for the  
25 patients suffering from AP. In addition, no calorie restriction/order has been described. Therefore  
26 both groups can be regarded as being treated within accepted practice recommendations.  
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30 In this study, early high energy administration will be the intervention. Patients will be randomized  
31 to group A or B: see Figure 2.  
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39 **Groups:** In **group A**, high energy will be delivered after admission. Patients will receive a 10 Ch  
40 nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will be immediately started as  
41 follows: On Day 0 (from admission until the start of EN (can vary from 2-24 h)): calorie intake will  
42 be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until  
43 the oral feeding starts. In **group B**, low energy administration after hospital admission. Patients will  
44 receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until  
45 the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10  
46 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until  
47 the oral feeding starts. However, between groups A and B only the amount of calories administered  
48 will be different. Patients will receive the same amount of fluid and ions during EN (see below).  
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**Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

**Energy:** 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate:** 18.3g (49%E), **Fat:** 5.8g (35%E) + **Minerals:** 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).

**Zero Energy Enteral Tube Feed (100ml):**

**Energy:** 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate:** 0g, Fat: 0g + **Minerals:** 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride (0%E) (in this study the local institutional pharmacy will provide it in accordance with the Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture of the above-mentioned two solutions will be used.

**Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

**Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for 24 h and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing ones) orally plus enteral tube feed (440ml, 720 kcal/day) will be started on the day when: (1) abdominal pain has been ceased for at least 6 h before the new day started, (2) CRP level has started decreasing and are below 100 mg/L and (3) amylase or lipase level has started decreasing

**Start of total feeding** (around 2000kcal): If the patients have no symptoms during the mixed oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding (according to local policy) can be started.

**Other issues:** The speed of EN will be different for the patients (depends on the body weight), however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties reaching the 30

1 kcal/kg/day calories intake (if the patient's body weight is above 75 kg) additional intravenous  
2 calorie will be added using Sterofundin G. Maximum of 2000 ml (= 400 kcal) can be delivered in  
3 this way. If NG feeding is not tolerated, NG tube will be replaced to NJ tube as described above. If  
4 NJ feeding is not tolerated, EN will be reduced by 50% and increased again gradually until  
5 tolerated. If the re-increasing process is still not tolerated total parenteral nutrition (TPN) will be  
6 started to reach the required energy target. In case of SAP, TPN has to be delivered via central  
7 venous catheter.  
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### 20 **11. Other treatment of subjects**

21 General treatment indicated by the IAP/APA guideline will be utilized[53].  
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### 26 **12. Discharge of patients**

27 Uniformization of the length of hospital stay is necessary to avoid bias concerning LOH. Re-  
28 admission within one week after discharge has to be considered as the same hospital admission.  
29 Patients has to be counted as discharged from hospital/from the study when (1) the total feeding  
30 was tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP  
31 level is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-  
32 related complication requiring hospitalization is detected.  
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### 44 **13. Endpoints**

45 The following primary endpoints will be calculated: A combination of MOF more than 48h and  
46 Mortality. The following secondary endpoints will be analyzed: (1) pancreatic necrosis, (2)  
47 nutrition related complications: diarrhoea, aspiration pneumonia, pneumothorax due to central TPN  
48 catheter placement, (3) need for conversion from NG to NJ feeding tube (4) need for conversion  
49 from EN to TPN, (5) days until the start of total feeding, (6) use of antibiotics, (7) pain relapse, (8)  
50 CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission,  
51 (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation. Notably,  
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1 only direct costs will be calculated that include all medications, services, salaries of healthcare  
2 professionals, equipment and day care costs.  
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#### 8 **14. Monitored parameters during hospitalization**

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10 There will be a large variety of parameters monitored during the study (e.g. medical history,  
11 physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A will  
12 contain the parameters collected on admission. Form B will contain parameters collected every day  
13 during hospitalization. Form C will contain parameters collected 1 month after hospital discharge.  
14 For details see supplementary materials or web page (<http://www.pancreas.hu/en/studies/goulash>),  
15 which will be available from February 2017. Data collection on the case report form (CRF) will be  
16 done electronically (see data management).  
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#### 28 **15. Data management and statistical analyses**

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30 **Data handling:** Data will be handled by IDMB. Electronic CRF (eCRF) will be used. The  
31 Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data  
32 flow will be described in Data Management Plan (DMP). Data from completed eCRFs will be  
33 validated under the direction of the Data Manager at IDMB according to Data Cleaning Plan  
34 (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to  
35 the Investigator using a data query form (DQF), and be documented for each individual subject  
36 before clean file status is declared. All changes to eCRF will be recorded. Before Data Base Lock  
37 Data Review Meeting will decide and document necessary steps related to any issue in the database  
38 and define the analysis sets. Member of the data review meeting are delegated investigator,  
39 biostatistician and data manager. Adverse events (AEs) will be coded using MedDRA. AdWare  
40 Research Ltd., who will act as IDMB, works according to GCP, GLP, FDA 21CFR PART11 and  
41 other relevant regulatory requirements. AdWare Ltd. has GLP and ISO 9001 certificates.  
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**Study populations:**

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2 Three analysis populations will be defined:

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4 Safety Analysis Set (SAS): all patients enrolled in the study.

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6 Per Protocol Set (PPS): all enrolled patients who finished the study conforming to the  
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8 requirements of the Study Protocol.

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10 Intention to Treat (ITT) all randomized participants who start on a treatment, excluding  
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12 consent withdrawals.

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17 **Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit  
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19 recommendation for dropouts from the PPS group with reasons given to SC. All recommendations  
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21 will be filed. SC will discuss all the information and if the alteration in the protocol would be  
22  
23 expected to have any bearing on the interventions and outcomes of the study, the patient will not be  
24  
25 included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be  
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27 ordered if: (1) any of the exclusion criteria diagnosed during the course of AP, (2) at least 50% of  
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29 the energy requirement is not achieved on any days during the study, (3) parameters required for  
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31 answering the primary endpoints are missing or (4) serious medical reasons not related to  
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33 pancreatitis (i.e. accidents, stroke) occur.  
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39 **Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later)  
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41 statistical packages; Microsoft MSWord will be used for reporting.  
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46 **Statistical Methods:** Baseline patient and disease characteristics will be analyzed by using  
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48 descriptive analysis. Demographic and baseline characteristics will be summarized for the overall  
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50 study population. Continuous variables will be described by mean, median, standard deviation, and  
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52 ranges and categorical variables will be described by absolute and relative frequencies. A graphical  
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54 presentation of efficacy variables will be prepared, if applicable. Descriptive statistics for both of  
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56 the primary and secondary parameters will be analyzed similarly. Mean changes (and their 95% CI)  
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58 from baseline to end-of-study visit will be presented as well. Chi-squared tests will be applied to  
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1 compare proportions between the different groups. Mortality/extended MOF will be investigated  
2 using the Kaplan-Meier analysis method; while subgroup comparisons will be performed using the  
3 Chi-squared or Fisher's exact test, as appropriate. For safety data, descriptive statistics and  
4 individual listings of adverse events will be also presented.  
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12 **Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under 40y,  
13 40y-59y, 60y-80y), (2) BMI (below 20, 20-24, 25-29, 30-35, above 35), (3) the start of abdominal  
14 pain before admission ( $\leq 24$ h, 24-48h,  $\geq 48$ h), (4) severity of the disease SAP and MAP. All  
15 subgroup analyses, (5) etiologies will be done descriptively. No confirmatory statistical testing will  
16 be applied. Hence, statistical tests and the p-values attached to them will be regarded as descriptive  
17 and not as tests of hypotheses.  
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20 Details of the applied statistical tests will be described in the Statistical Analysis Plan.  
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## 26 27 28 29 30 31 **16. Early quality assessment.**

32 Early quality assessment check will be performed on the first 100 patients. IDMB (AdWare Ltd.)  
33 will perform an independent assessment of the trial related documents and activities, with the aim  
34 of ensuring the respect of subject's right, safety and well-being and to guarantee the plausibility of  
35 clinical data. The similarity of groups at baseline will be also checked. IDMB will report to SC. SC  
36 will discuss all the information and if the differences would be expected to have any bearing on the  
37 interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of  
38 all participants who were randomized or allocated into each group or the differential dropout rate is  
39 above 15 percent between the arms, the study needs to be reassessed and IDMB will make  
40 recommendations regarding either reevaluation of power calculation, extension of recruitment  
41 period, extension of number of study centers or termination of trial.  
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## 58 59 60 **17. Interim analyses and premature termination of the study.**

1 IDMB can also recommend to stop the trial early for ethical reasons if one of the groups clearly  
2 shows evidence of a significant benefit. An interim analysis will be performed on the primary  
3 endpoint when 50% of patients have been randomized and discharged from the hospital. The  
4 interim analysis will be performed by the IDMB. IDMB will report to SC.  
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10 The Haybittle–Peto boundary approach will be used. If the interim analysis shows a probability of  
11 equal to, or less than 0.001 that a difference as extreme between the treatments is found, given that  
12 the null hypothesis is true, then the trial will be stopped early.  
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### 20 **18. Centres**

21 The trial will start in two centres (University of Debrecen and University of Pécs), after which the  
22 study is open for other centres. In all cases IDMB will make an audit of the centre and will report to  
23 the SC. SC keeps the right to decide whether the centre meets the required quality to join the study.  
24 Compulsory requirements for a centres: (1) it needs to treat at least 50 AP patients a year, (2) it  
25 needs to have all the equipment required for the study, (3) besides the regular medical team the  
26 centre has to appoint at least one doctor and one nurse/administrator fully available for the trial with  
27 no additional commitments which can interfere with her/his duty when her/his availability is  
28 required, (4) the blinding described above can be fully utilized, (5) all persons need to attend a  
29 preliminary meeting where all the details concerning the studies are discussed fully and have  
30 qualified as investigators in a GCP course. Centres wish to join need to send a letter of intent to the  
31 corresponding author by e-mail.  
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### 48 **19. Publication policy**

49 Centres providing more than 25 patients can provide two authors to the authorship list. Every  
50 additional 25 patients will give the opportunity to nominate an additional author.  
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### 58 **20. Feasibility**

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As a general protocol for the treatment of AP at the Centre for Translational Medicine at the University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the Emergency Department. Patients data between the period of 1 January – 31 May 2016 were analyzed and the following observations were noted: (1) In 85% of all AP admission early EN could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients tolerated NG feeding without any complications. The rest of the patients who had gastric retention or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature data described in the introduction. Concerning the number of patients at the University of Pécs around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore, if no other Institution would join the study it can be completed within 3 years.

## 21. Safety

Since no unknown drugs/therapy are used in the study no adverse and serious adverse events (SAE) are expected/interpretable that would be attributable to the intervention during the trial. In this trial IDMB will examine safety variables after every 16 patients have completed. Moreover, investigators will report AE or SAE via a separate form which has to be sent to IDMB and 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>.

## 22. Additional information and future plan.

1 Blood samples (serum and plasma) will be stored from all patients in order to study laboratory  
2 parameters later if required (e.g. the laboratory could not measure it), and in order to build up a  
3 biobank for later clinical studies to which all participants will be given informed consent. The  
4 samples will be stored on -80°C. A follow-up study (called GOULASH PLUS) is under preparation  
5 in order to follow the patients for up to 5 years after the study. The study protocol will also be  
6 published.  
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## 17 DISCUSSION

18 Here we report the protocol of a prospective double-blind RCT to study the effects of early energy  
19 restoration in AP. The pre-clinical studies [1, 9] and meta-analyses suggest that early energy  
20 supplementation should be beneficial. Our main hypothesis is that elevating the energy level of  
21 acinar and ductal cells will prevent these cells from injury, therefore, it will decrease the extent of  
22 necrosis during AP. Since both the local and systemic complications (immune response) largely  
23 depend on the extent of the necrosis we propose that this intervention will reduce multi-organ  
24 failure and mortality in AP as well. Although nutritional interventions for patients with mild  
25 pancreatitis are probably not needed, we must involve all AP patients into the study. It has to be  
26 highlighted that the main aim of the study is not to find new treatments in MAP or SAP, but to  
27 prevent the development of SAP. This is the reason why severity cannot be a selection criteria but  
28 has to be the primary endpoint. Concerning ethical issues, this study has very low risk for patients.  
29 The enteral solution (Nutrison Energy) used in this study is widely used in several diseases related  
30 malnutrition in patients and has almost no contraindications, therefore no adverse events are  
31 expected during the trial. It is almost needless to say that at the end of the project we will  
32 disseminate our results in the medical community. We will publish our results in an open access  
33 way.  
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**CONCLUSION**

This study provides the first and type A evidence concerning the necessity of energy intake for patients suffering from AP.

**List of abbreviations**

AE – adverse event

AP – acute pancreatitis

BMI – body mass index

CRF – case report file

CRP – C-reactive Protein

DCP – data cleaning plan

DMP – data management plan

DQF – data query form

eCRF – electronic clinical report form

EN – enteral nutrition

GOULASH – name of the study: general utilization of early energy administration in acute pancreatitis.

HPSG – Hungarian Pancreatic Study Group

ICU – intensive care unit

IDMB – Independent data management and biostatistics provider company

ITAB – International Translational Advisory Board

ITT – Intention to Treat

LOH – length of hospital stay/hospitalization

MAP – mild and moderate AP

MOF – multi organ failure

NG – nasogastric

1 NJ – nasojejunal

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3 PCT – procalcitonin

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6 PN – parenteral nutrition

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8 PPS – Per Protocol Set

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10 SAE – severe adverse event

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12 SAS – Safety Analysis Set

13  
14 SAP – severe AP

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16 SC – Steering Committee

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18 TPN – total parenteral nutrition

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21 WBC – white blood cell count

## 22 23 24 25 26 **Declarations**

27  
28 The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical  
29 approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research  
30 Ethics Committee of the Medical Research Council.  
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34 This protocol is the first version of the trial completed on 24th May 2017.  
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## 37 **Availability of data and materials**

38  
39 Not applicable, because the trial has not completed patient recruitment.  
40  
41

## 42 **Competing interest**

43  
44 The authors declare that they have no competing interests.  
45  
46

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51 and Innovation Office (GINOP-2.3.2-15-2016-00015). Since no additional treatment is necessary  
52 for the study, the general healthcare costs are covered by the National Healthcare System.  
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### Authors' contributions

All authors were involved in the study design, edited the manuscript, read and approved the final manuscript. During the study KM, ANS, DP and PV are going to randomize the patients, obtain the consent form and ensure the blinding. AM, KS, JB, SG, MP, PS, ZV and TT are going to manage the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will prepare the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS will be members of SC. PH and KM drafted the manuscript.

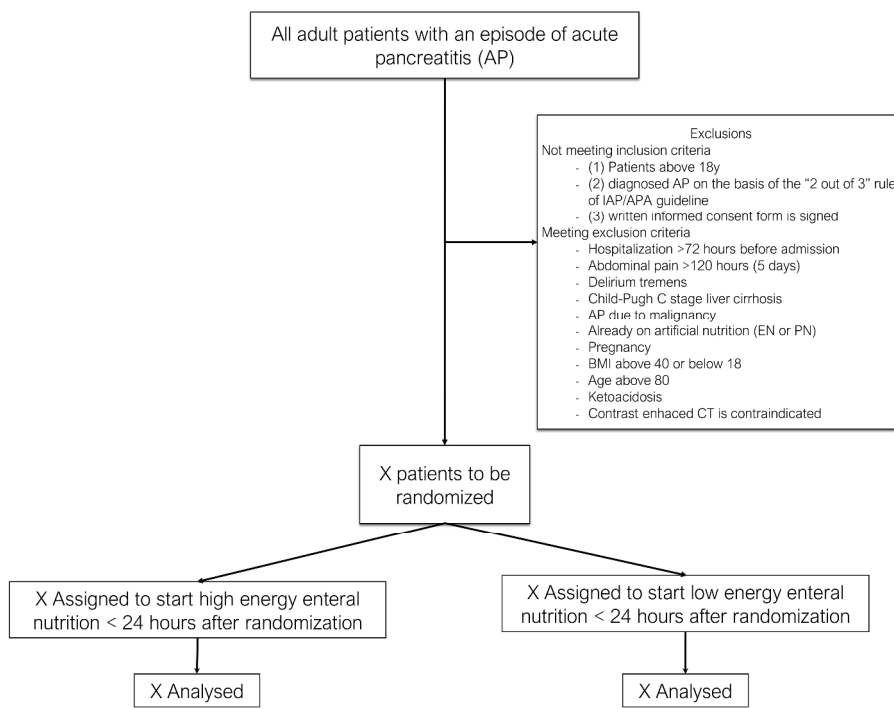
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Flow of participants

361x270mm (300 x 300 DPI)

ew only

TIMEPOINT**	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
	<24h	0	day1	day2	day3	dayx	discharge	1m after discharge
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Laboratory test	X							
CT examination	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
High energy administration			←————→					
Low energy administration			←————→					
<b>ASSESSMENTS:</b>								
Questionnaire A		X						
Questionnaire B			X	X	X	X	X	
Questionnaire C								X

Intervention. Patients will be randomized to group A (high energy) or B (low energy)

194x169mm (300 x 300 DPI)

# FORM-A

# Acute Pancreatitis

# GOULASH

**The physical examination has to be done ON ADMISSION!**  
**The blood for laboratory parameters has to be drawn ON ADMISSION!**  
**This form has to be filled ON ADMISSION!**

## Questionnaire

### 1. Patient personal details

Insurance number:.....  
 First name:.....  
 Last name: .....,  
 Date of birth:.....  
 Gender: female male  
 Ethnicity/Race: White / Black / Asian-Indian Not known

### 2. Details from the medical history

**Alcohol consumption:** yes / no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/day):.....  
 since when? (years):.....  
 Alcohol consumption in the last 2 weeks: .....,  
 if not:  
 Did you drink alcohol earlier? yes/no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/occasion):.....  
 For how many years?.....  
 How long ago did you stop drinking alcohol?.....

*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

**Smoking:** yes / no  
 if yes: amount (cigarettes/day):.....  
 For how many years? .....,  
 if not:  
 Did you smoke earlier? yes/no  
 if yes: amount (pcs/occasion):.....  
 For how many years?.....  
 How long ago did you stop smoking? .....,

**Drug abuse:** yes / no *Prescribed medication should not be included here.*  
 if yes: type of drug:..... amount:.....  
 since when (year):.....  
 (if there are more drugs, please describe them in the NOTES section at the end)

**Diabetes mellitus:** yes / no  
 if yes: type: Type I. / Type II./Type III. c / MODY  
 since when (year):.....

Country:
Town:
Hospital:
Doctor:
Patient No:

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## FORM-A

Acute  
Pancreatitis

## GOULASH

**Lipid metabolism disorder:** yes / no

if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no

*Not counting the current episode.*

if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other

if other: please describe:.....

If the patient had ACUTE PANCREATITIS in the history:

How many times did the patient have acute episodes before this episode:.....

When did the patient have the first acute episode (year):.....

If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:

When was it diagnosed?.....

How many times did the patient have acute episodes before this episode:.....

When did the patient have the first acute episode (year):.....

If the patient has PANCREATIC CANCER::

When was it diagnosed?.....

Was the patient diagnosed with chronic pancreatitis? yes / no

If yes, when was it diagnosed?.....

How many times did the patient have acute episodes before this episode?:.....

When did the patient have the first acute episode (year):.....

Other information:

.....

**Pancreas disorders in family history:**

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:.....

.....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data

if yes: please describe:.....

**Other illnesses:** yes / no

if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

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**Principal Investigator:**

Kata Márta **Tel:** +36 20 211 5868 **e-mail:** k.marta@tm-pte.org

# Acute

# GOULASH

## FORM-A

## Pancreatitis

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

**Diet:** yes / no  
 if yes: please describe:.....

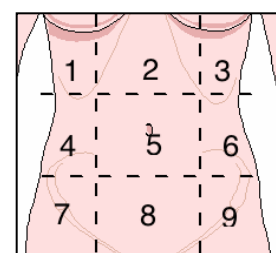
**3. Etiology** *The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to "Idiopathic" if etiological factor was not identified.*

Biliary	yes	no	no data
Alcohol	yes	no	no data
Virus infection	yes	no	no data
Trauma	yes	no	no data
Drug-induced	yes	no	no data
Congenital anatomical malformation	yes	no	no data
Cystic fibrosis	yes	no	no data
Gluten-sensitive enteropathy	yes	no	no data
Hypertriglyceridaemia	yes	no	no data
Genetic	yes	no	has not been tested yet
Idiopathic	yes	no	
Other	yes	no	

if yes: please describe:.....

**4. Complains, symptoms**

**Abdominal pain:** yes / no  
 if yes: since when (hours):.....  
 type: cramping / dull / sharp  
 intensity (1-10):.....  
 location: diffuse / localized  
 Please mark the location!  
 radiation:.....



**Nausea:** yes / no

**Vomiting:** yes / no  
 if yes: how many times:.....  
 contents of cast:.....

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**FORM-A****Acute  
Pancreatitis****GOULASH****Subfebrility/fever:** yes / no

if yes: since when:.....

degree (°C):.....

**Appetite:** good / retained / bad**Weight loss:** yes / no

if yes: how much (kg):.....

How long did it take? (weeks):.....

**Jaundice:** yes / no

if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus*Please refer to the period just before your symptoms has started.***5. Admission details and state****Blood pressure (Hgmm):**.....**Heart rate (/minute):**.....**Body weight (kg):**.....**Body height (cm):**.....**Respiratory rate (/minute):**.....**Body temperature (°C):** .....

axillary/rectal

**Oxygen saturation (%):** .....

Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no**Abdominal guarding:** yes / no**Jaundice:** yes / no**Glasgow Coma Scale (GCS):**.....**Glasgow Coma Scale:****Eye response**

4 points: Spontaneous eye opening

3 points: Eye opening in response any speech

2 points: Opening to response to pain

1 point: No eye opening

**Verbal Response**

5 points: Orientated

4 points: Confused conversation

3 points: Inappropriate speech

2 points: Incomprehensible speech

1 point: No verbal response.

**Motor Response**

6 points: Obeying command

5 points: Localizing response to pain

4 points: Withdraws to pain

3 points: Decorticate posture

2 points: Decerebrate posture

1 point: No response to pain

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**FORM-A****Acute  
Pancreatitis****GOULASH****6. Laboratory parameters on admission****OBLIGATORY PARAMETERS:**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
Serum glucose (mmol/l)	
Hemoglobin A1C (%)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
C-reactive protein (mg/l)	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	

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## FORM-A

Acute  
Pancreatitis

## GOULASH

## - CTSI:

## I. Pancreas

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

## II. Size of Necrosis

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

## III. Extrapancreatic findings

- presence of extrapancreatic findings

## DETAILED REPORT

## - 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** (nonenhancement):

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60% , above 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

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# FORM-A

# Acute Pancreatitis

# GOULASH

**12. Epicrisis** *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
.....

### NOTES

.....  
.....

### DATE:

YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION:            HOUR ..... MIN: .....

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ..... **SIGNATURE:** .....

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ..... **SIGNATURE:** .....

For peer review only

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# Acute

# FORM-B

# Pancreatitis

# GOULASH

PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY

**Day No:**

**Date (+hour, min)**

**GOULASH No:**

(Automatically generated)

## 1. Patient personal details

First name:.....

Last name: .....

## 2. Complains, symptoms

**Abdominal pain:** yes / no

if yes: since when (hours):.....

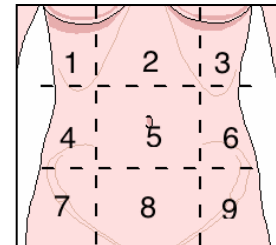
type: cramping / dull / sharp

intensity (1-10):.....

location: diffuse / localized

Please mark the location!

radiation:.....



**Nausea:** yes / no

*If YES, retention measurement has to be performed.*

**Vomiting:** yes / no

*If YES, NG tube has to be replaced by NJ tube.*

**Subfebrility/fever:** yes / no

if yes: since when:.....

degree (°C):.....

**Appetite:** good / retained / bad

**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

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**FORM-B****Acute  
Pancreatitis****GOULASH****3. Patient's state**

Blood pressure (Hgmm):.....

Heart rate (/minute):.....

Body weight (kg):.....

Respiratory rate (/minute):.....

Body temperature (°C): .....

axillary/rectal

Oxygen saturation (%): .....

O2 therapy: yes/no

Abdominal tenderness :      yes / no

Abdominal guarding:              yes / no

Jaundice:                              yes / no

Glasgow Coma Scale (GCS):.....

**Glasgow Coma Scale:****Eye response**

4 points: Spontaneous eye opening

3 points: Eye opening in response any speech

2 points: Opening to response to pain

1 point: No eye opening

**Verbal Response**

5 points: Orientated

4 points: Confused conversation

3 points: Inappropriate speech

2 points: Incomprehensible speech

1 point: No verbal response.

**Motor Response**

6 points: Obeying command

5 points: Localizing response to pain

4 points: Withdraws to pain

3 points: Decorticate posture

2 points: Decerebrate posture

1 point: No response to pain

**4. Laboratory parameters****OBLIGATORY PARAMETERS**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

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2



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# FORM-B

# Acute Pancreatitis

# GOULASH

**OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	
IgA (g/l)	
IgM (g/l)	
IgG (g/l)	
IgG4 (g/l)	
CA 19-9 (U/ml)	
PaO <sub>2</sub> (Hgmm)	
HCO <sub>3</sub> (mmol/l)	
sO <sub>2</sub> (%)	
sweat chloride (mmol/l)	
urine amylase	
urine lipase	
urine creatinine	
(other)	

**Blood glucose (by finger stick test) *Compulsory on the first day:***

4h	mmol/l	amount of insulin if administered : ..... IU
8h	mmol/l	
12h	mmol/l	
16h	mmol/l	
20h	mmol/l	
24h	mmol/l	

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# FORM-B

# Acute Pancreatitis

# GOULASH

### 5. Imaging (if performed)

yes no

#### Abdominal ultrasonography:

yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

- **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:

.....  
.....

#### Abdominal X-ray:

yes no

Description:

.....  
.....

#### Chest X-ray:

yes no

Description:

.....  
.....

#### Chest Computed Tomography:

yes no

Description:

.....  
.....

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## FORM-B

Acute  
Pancreatitis

## GOULASH

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:

## I. Pancreas

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

## II. Size of Necrosis

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

## III. Extrapancreatic findings

- presence of extrapancreatic findings
- 

## DETAILED REPORT

## - 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 (nonenhancement):

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

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

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# FORM-B

# Acute Pancreatitis

# GOULASH

- Distant **abdominal fluid**:
  - o Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - o Moderate amount (easy to see, but without pelvic or abdominal distension)
  - o Large amount with abdominal/pelvic distension
  
- **Pleural effusion**:
  - o none
  - o one sided:..... (AP diameter: ..... cm)
  - o Both sides, L - ..... cm, R - ..... cm
  
- **Extrapancreatic findings**:
  - o Inflammation (Cholecystitis, Duodenitis, etc.) location: .....
  - o Cholecystolithiasis
  - o Choledocholithiasis
  - o Signs of bowel ischaemia
  - o Bowel distension, ileus
  - o Venous thrombosis
  - o Pseudoaneurysm
  - o Parenchymal organ involvement, define: .....

Other Description:

.....

.....

## 6. Microbiology examination

Biological sample collection                      yes                      no

If yes:                      place: /blood, urine, airway, pancreas, other/

result:                      .....

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# FORM-B

# Acute Pancreatitis

# GOULASH

**Pain management:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:**                    yes    no

if yes,

name of the medication:.....

dosage:.....

**Intensive care:**        yes    no

if yes,

namely (ventilation, vasopressor therapy):.....

**Other:**

if yes,

please describe:.....

.....

.....

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# Acute

# FORM-B

# Pancreatitis

# GOULASH

### 8. Interventions, endoscopic treatment:

yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage  
 Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent  
 Early complications: none/bleeding/perforation

ERCP: yes no

if yes:  
 Successful biliary cannulation: yes no if yes: notes: .....  
 Precut: yes no if yes: needleknife/precut papillotomy  
 EST: yes no if yes: biliary/pancreatic  
 Stone extraction: yes no  
 Stent: yes no if yes: metal/plastic  
 How many pcs? diameter(Fr)? length(cm)?  
 Pancreatic duct filling: yes no if yes: notes: .....

### 9. Complications

Pancreatic: yes no no data  
 if yes, fluid collections / pseudocyst / necrosis / diabetes  
 Organ failure: yes no  
 if yes, lung / heart / kidney /other  
 Duration of organ failure: <48 hours >48 hours  
 Death: yes no  
 if yes: the exact time of death: ..... e.g. 10.25 or 22.45

### NOTES

.....  
 .....  
 .....

### DATE:

YEAR: ..... MONTH: ..... DAY: .....

NAME OF THE DOCTOR: .....SIGNATURE: .....

NAME OF THE NURSE: .....SIGNATURE: .....

NAME OF THE SCIENCE ADMINISTRATOR: .....SIGNATURE: .....

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**FORM-C****Acute  
Pancreatitis****GOULASH****Questionnaire****1. Patient personal details**

First name:.....

Last name: .....

GOULASH No:

(Automatically generated)

**2. Details from the medical history (in the last month)**

**Alcohol consumption:** yes / no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/day):.....

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

**Smoking:** yes / no  
 if yes: amount (cigarettes/day):.....

**Drug abuse:** yes / no *Prescribed medication should not be included here.*  
 if yes: type of drug:..... amount:.....  
*(if there are more drugs, please describe them in the NOTES section at the end)*

**Any re-hospitalization?:** yes / no

if yes:                      cholecystectomy:      yes      no  
    recurrent AP:                      yes      no  
    other:                                      .....

**Medications taken regularly in the last month:** yes / no

*Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*

if yes:  
 name:.....active substance:.....dose(gram,milligram, etc.).....  
     if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
     if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
     if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....



# FORM-C

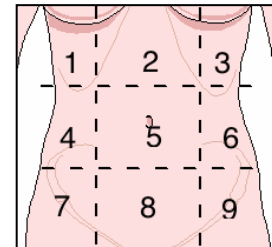
# Acute Pancreatitis

# GOULASH

**Diet:** yes / no  
 if yes: please describe:.....

### 3. Complains, symptoms

**Abdominal pain:** yes / no  
 if yes: since when (hours):.....  
 type: cramping / dull / sharp  
 intensity (1-10):.....  
 location: diffuse / localized  
 Please mark the location!  
 radiation:.....



**Nausea:** yes / no

**Vomiting:** yes / no  
 if yes: how many times:.....  
 contents of cast:.....

**Subfebrility/fever:** yes / no  
 if yes: since when:.....  
 degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no  
 if yes: how much (kg):.....  
 How long did it take? (weeks):.....

**Jaundice:** yes / no  
 if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

### 4. Laboratory parameters

#### OBLIGATORY PARAMETERS

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

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## FORM-C

Acute  
Pancreatitis

## GOULASH

**OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	

**5. Imaging examination**

**Abdominal ultrasonography:**                      yes                      no

Description:

**Ultrasound:**

- **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)

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# FORM-C

# Acute Pancreatitis

# GOULASH

- Size of peripancreatic fluid or pseudocyst: ..... cm
- **Pancreas homogeneity:**
  - o Homogenous
  - o Inhomogeneous, includes area(s) of low echogenicity
  - o Inhomogeneous, includes calcifications
- In case of circumscribed low echogenicity area, it's size: ..... cm
- **Wirsung** dilatation: YES / NO (yes, diameter: ..... mm)

Other Description:

.....  
 .....

**Abdominal Computed Tomography:**    yes                      no  
 Modified CTSI Score:    .....0-10.....

*Please NOTE! Abdominal CT is compulsory if*  
*- Abdominal ultrasonography is not fully completed OR*  
*- There is any alteration on abdominal ultrasonography*

**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:**
  - I. Pancreas**
    - o Normal pancreas
    - o Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
    - o pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
  - II. Size of Necrosis**
    - o Necrosis absent
    - o < 30% necrosis
    - o > 30% necrosis
    - o > 60% necrosis
  - III. Extrapancreatic findings**
    - o presence of extrapancreatic findings

### DETAILED REPORT

- **Pancreas Size:**
  - o Normal
  - o Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)



# FORM-C

# Acute Pancreatitis

# GOULASH

- 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** (nonenhancement):
  - Largest diameter of necrosis area: ..... cm
  - Location of necrosis: .....
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 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
  - Choledocholithiasis
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: .....

Other Description:

.....  
.....

# FORM-C

# Acute Pancreatitis



**6. Complications** *Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:**                    yes                    no                    no data  
 if yes:                    fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:**            yes                    no  
 if yes:,                    lung /heart / kidney /other

**Death:**                    yes                    no  
 If yes: the exact date of death: ..... e.g. 10.25 or 22.45

**7. Epicrisis** *A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
 .....

**DATE:**  
 YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

**NAME OF THE DOCTOR** : .....**SIGNATURE:** .....

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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	2,17_____
	2b	All items from the World Health Organization Trial Registration Data Set	17_____
Protocol version	3	Date and version identifier	17_____
Funding	4	Sources and types of financial, material, and other support	17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,18_____
	5b	Name and contact information for the trial sponsor	5_____
	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	5, 17_____
	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)	5, 12 13_____

1  
2  
3 **Introduction**  
4

5 Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	3, 4 15, 16_____
6 rationale		studies (published and unpublished) examining benefits and harms for each intervention	
7			
8	6b	Explanation for choice of comparators	4_____
9			
10 Objectives	7	Specific objectives or hypotheses	4_____
11			
12 Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
13		allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4, 6_____
14			

15  
16 **Methods: Participants, interventions, and outcomes**  
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18 Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	13, 10_____
19		be collected. Reference to where list of study sites can be obtained	
20			
21 Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	6, 13_____
22		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
23			
24 Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	7, 8, 9_____
25		administered	
26			
27	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	9_____
28		change in response to harms, participant request, or improving/worsening disease)	
29			
30	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	14_____
31		(eg, drug tablet return, laboratory tests)	
32			
33	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9_____
34			
35 Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	9, 10, 11, 14_____
36		pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
37		median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
38		efficacy and harm outcomes is strongly recommended	
39			
40			
41 Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	7, 10_____
42		participants. A schematic diagram is highly recommended (see Figure)	
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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_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6_____

**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	6, 7_____
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	7_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, 18_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7_____
	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	10, 11, 12, 13, 14, 15__
	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, 10_____

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3	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	10_____
4				
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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	11, 12, 13_____
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13_____
11				
12		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)	10, 11, 12_____
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16	<b>Methods: Monitoring</b>			
17				
18	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	6, 10, 12_____
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23		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	13, 14_____
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26	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	14_____
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14, 6, 10, 12_____
30				
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33	<b>Ethics and dissemination</b>			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 17_____
36				
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38	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)	14_____
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, _____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15 _____
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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	10 _____
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 _____
13				
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15	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	2 _____
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18	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	14 _____
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21	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	2 _____
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	13 _____
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2 _____
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30	<b>Appendices</b>			
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32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
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35	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	15 _____
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): Protocol of a multicentre randomized double-blind clinical trial

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**High versus low energy administration in the early phase of acute pancreatitis (GOULASH  
trial): Protocol of a multicentre randomized double-blind clinical trial**

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Word count: 6548

**ABSTRACT**

**Introduction.** Acute pancreatitis (AP) is an inflammatory disease with no specific therapy. Mitochondrial injury followed by ATP depletion in both acinar and ductal cells is a recently discovered early event in the pathogenesis. Importantly, preclinical research showed that intracellular ATP delivery restores the physiological function of the cells and protects from cell injury suggesting that restoration of energy levels in the pancreas is therapeutically beneficial. Despite several, high quality and experimental observations in this area, no randomized trials have been conducted to date to address the requirements for energy intake in the early phase of AP.

**Methods/Design.** This is a randomized, controlled two-arms double-blind multicentre trial. Patients suffering from AP will be randomly assigned to groups A (30 kcal/kg/day energy administration starting within 24h of hospital admission) or B (low energy administration during the first 72h of hospital admission). Energy will be delivered with nasogastric tube feeding with additional intravenous glucose supplementation or total parenteral nutrition if necessary. A combination of multi organ failure for more than 48h and mortality is defined as the primary endpoint, whereas several secondary endpoints such as length of hospitalization or pain will be determined to elucidate more detailed differences between the groups. The general feasibility, safety and quality checks required for high quality evidence will be adhered to.

**Ethics and Dissemination.** The study has been approved by the relevant organization, The Scientific and Research Ethics Committee of the Hungarian Medical Research Council (55961-2/2016/EKU). This study will provide evidence whether early high-energy nutritional support is beneficial in the clinical management of AP. The results of this trial will be published in an open access way and disseminated among medical doctors.

**Trial registration:** The trial has been registered at the ISRCTN (ISRCTN 63827758).

**Keywords:** acute pancreatitis, energy administration, enteral feeding, randomized clinical trial

## ARTICLE SUMMARY

### Strengths and limitations of this study

- Strength 1; This is a randomized controlled two-arms double-blind multicentre trial which provides the first type A evidence concerning the necessity of early energy intake for patients suffering from AP.
- Strength 2; The study enjoys continuous support from an International Translational advisory board (ITAB) including several well established experts.
- Strength 3; Data will be separately handled by an Independent Data Management Board (IDMB).
- Strength 4; There are no unknown drugs/therapy used in the study, therefore no adverse and serious adverse events are expected.
  
- Limitation 1; In order to detect a treatment effect of at least 50% of the early treatment, a sample size of 957 subjects will be necessary to be recruited which delay the final conclusion of the study.
- Limitation 2; The double-blind arrangement of the study requires many staff member working on the project which may limit the number of joining centres.

## BACKGROUND

Acute pancreatitis (AP) is an inflammatory disease of the exocrine pancreas, which is life threatening in its severe form. Unfortunately, while the overall mortality of AP is around 2-5%, and in its severe form 25-57%, no specific therapy is available. Besides the limited interest of pharmacological companies the main reasons are (i) the small number of research teams in the field and (ii) the lack of collaborations between basic and clinical scientists. Importantly, many new therapeutic targets were identified in the last decade with clear translational merits [1-8]. One of the main highlights among them is the discovery of energy depletion in the early phase of AP [1, 3-5, 7-17].

It has been shown that almost independently of the etiological factors the early phase of AP is almost the same. Bile acids, ethanol, fatty acids and the latter's metabolite fatty acid ethyl esters cause mitochondrial damage and ATP depletion in pancreatic ductal and acinar cells driving the cells to death and causing pancreatic necrosis [1, 3, 4, 10-14, 18-31]. Very importantly, restoration of ATP levels in both cell types prevented cell death and at least partially restored their function [1,



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2 9]. In experimental pancreatitis models the same observations have been revealed [10-21].  
3  
4 Although these experimental observations clearly suggest that restoration of energy level could be a  
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6 therapeutic tool in AP, this has not been translated into clinical trials.  
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8  
9 One of the best and most physiological way of delivering energy to a patient is enteral nutrition  
10 (EN). Not surprisingly, besides fluid resuscitation this is almost the only way to significantly reduce  
11 mortality in AP [22-33]. Recent analyses of prospectively collected data from 600 patients suffering  
12 from AP showed that the mortality is 27% with EN, versus 57% without EN in the severe form  
13 (SAP) [34]. Importantly EN not only decreases mortality but also reduces the frequency of multi-  
14 organ failure and the necessity of interventions in patients suffering from SAP [35]. No data are  
15 available on whether early or on demand nutrition/energy supply is beneficial in SAP. The recently  
16 published Dutch PYTHON study suggests that there is no difference on early versus on demand  
17 enteral tube feeding in SAP but patients may have received an insufficient amount of energy at the  
18 early phase of the disease [36, 37]. In the early EN group patients received over 20 kcal/kg/day only  
19 from the third day onwards whereas in the on demand group they received energy supplementation  
20 only from day six[37]. In mild and moderate AP (MAP) much less information is available  
21 concerning the usefulness of EN. There are a large variety of protocols on EN in MAP. Immediate  
22 oral feeding [38], nasojejunal feeding [39-41] and nasogastric feeding [42][43] were all used.  
23 Notably immediate oral feeding significantly decreased the length of hospital stay (LOH) [38].  
24 Early (within 24h) nasogastric EN was not only well tolerated but reduced the intensity and  
25 duration of abdominal pain, decreased the necessity for opiates and almost completely eliminated  
26 the risk of oral food intolerance [42]. In order to obtain higher evidence of the usefulness of early  
27 EN in MAP and SAP we performed a systematic review and meta-analysis which showed that early  
28 EN can be beneficial in both, MAP and SAP [35]. However, we also realized the lack of  
29 multicentre randomized control trials addressing energy intake in the early phase of AP.  
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33 The main objective of this trial is to understand whether early energy supplementation to patients  
34 suffering from AP is beneficial. Our hypothesis is that early energy supplementation will prevent  
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the cells from death or decrease the size of necrosis if occur. This will decrease systemic immune response that will be ended in lower frequency of multi organ failure (MOF) and mortality. To prove this concept a randomized clinical trial involving all AP patients must be organized.

## METHODS

### 1. Design

This is a randomized controlled two-arms double-blind multicentre trial. Patients suffering from acute pancreatitis will be randomly assigned to groups A (high energy administration starting within 24h of hospital admission) and B (no energy administration after 24h of hospital admission).

### 2. Trial organization, committees and boards

GOULASH is designed and coordinated by the Centre for Translational Medicine at the University of Pécs and the Hungarian Pancreatic Study Group (HPSG). HPSG was established in 2011 in order to stimulate research in pancreatic diseases. Until now HPSG published the relevant guidelines of pancreatic diseases in order to improve patient care in the field of pancreatology [44-47] and has initiated four prospective clinical trials (EASY, PREPAST, APPLE and PINEAPPLE) [48-51].

The following committees and boards will be involved:

Steering committee (SC): The committee will be led by PH (gastroenterologist, internal medicine specialist). The members will be KM (medical doctor, full time employee on the project), ÁV (gastroenterologist, internal medicine specialist), ZM (intensive care specialist), TM (clinical research specialist) AS (multidisciplinary unit specialist), MP (gastroenterologist, internal medicine specialist), NF (radiologist), DK (surgeon), IB (interventional radiologist). SC will make decisions concerning all relevant questions including the drop outs during the study.

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2 International translational advisory board (ITAB): The committee will include gastroenterologist  
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4 (MML), surgeon (JPN) and basic scientists (MST, OHP). ITAB will continuously monitor the  
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6 progress of the study and will give advice to the SC.  
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11 The study was designed by SC and ITAB. The study is financially sponsored by the University of  
12  
13 Pécs, the Hungarian Academy of Sciences, and the National Research, Development and Innovation  
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15 Office. Neither sponsors were involved in the design of the study, and they will have no access to  
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17 the database management or to the randomization code.  
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### 21 **3. Study population**

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23 All patients diagnosed with AP will be informed of the possibility of taking part in the GOULASH  
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25 study. After the consent form is signed, a computer using a block randomization protocol will  
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27 randomize the patients (Figure 1).  
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31 **Inclusion criteria:** (1) Patients over 18y of age, (2) diagnosed AP on the base of the “2 out of 3”  
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33 criteria of the IAP/APA guideline[53] : (a) upper abdominal pain; (b) serum amylase or lipase >3x  
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35 upper limit of normal range; (c) characteristic findings on pancreatic imaging; however those  
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37 patients without abdominal pain will be excluded because the onset of AP cannot be determined, (3)  
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39 written informed consent form is signed.  
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43 **Exclusion criteria:** (1) Hospitalization 72 hours before admission, (2) abdominal pain >120 hours  
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45 (5 days), (3) delirium tremens, (4) Child-Pugh C stage liver cirrhosis, (5) AP due to malignancy, (6)  
46  
47 already on artificial nutrition (EN or PN), (7) pregnancy, (8) BMI above 40 or below 18, (9) age  
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49 above 80, (10) ketoacidosis, (11) whenever CT with contrast is contraindicated.  
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52 **Sample size:** Sample size calculation was based on the National Hungarian Registry operated by  
53  
54 the Hungarian Pancreatic Study Group. Our recent analyses indicated that MOF existing more than  
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56 48h arises in 9%, whereas mortality is in 2.8% of all patient suffering from AP [34]. Altogether  
57  
58 they represent around 10% of all AP patients. In order to detect a treatment effect of at least 50% of  
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1 the early treatment a sample size of 957 subjects will be necessary to be recruited using a 10%  
2 drop-out rate, 80% power and 95% significance level. The calculation was performed by the  
3 Independent data management and biostatistics provider company (IDMB, Adware Research LTD,  
4 Balatonfüred, Hungary).

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10 **Randomization:** In each centre participants will be divided into 2 groups receiving one of the two  
11 study treatments. The allocation of participants to the different groups will be carried out based on  
12 predefined randomization lists created separately for each recruiting centre. The randomization lists  
13 will be prepared with a block size of 4 and with an allocation ratio of 1:1.  
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#### 20 21 **4. Duration**

22 The planned starting date of the study is; 1 January 2017, and the planned finishing date of the  
23 study is; 1 January 2020.  
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#### 30 31 **5. Blinding**

32 The medical staff (e.g., taking the measurements such as blood pressure, examining health records  
33 for events such as abdominal pain, reviewing and interpreting examination results such as X-ray or  
34 CT) and the patient receiving the intervention will be blinded to knowledge of treatment  
35 assignment. The person providing the intervention cannot be blinded in this study. Sealed envelopes  
36 ensure the allocation sequence. Nutritional support equipment will be covered until the fourth day to  
37 ensure that only who made the randomization will know which group the patient was enrolled into.  
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#### 46 47 **6. Intervention**

48 Based on the currently available guidelines enteral feeding can be started at any time for the  
49 patients suffering from AP. In addition, no calorie restriction/order has been described. Therefore  
50 both groups can be regarded as being treated within accepted practice recommendations.  
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54 In this study, early high energy administration will be the intervention. Patients will be randomized  
55 to group A or B: see Figure 2.  
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**Groups:** In **group A**, high energy will be delivered after admission. Patients will receive a 10 Ch nasogastric (NG) or nasojejunal (NJ) feeding tube on admission. EN will be immediately started as follows: On Day 0 (from admission until the start of EN (can vary from 2-24 h)): calorie intake will be 0 kcal/kg/day. From Day 1 high energy enteral tube feed 30 kcal/kg/day will be provided until the oral feeding starts. In **group B**, low energy administration after hospital admission. Patients will receive a NG or NJ feeding tube at admission as described above. On Day 0 (from admission until the start of EN): calorie intake will be 0 kcal/kg/day. On day 1 0 kcal/kg/day, on day 2 10 kcal/kg/day, on day 3 20 kcal/kg/day and from day 4 30 kcal/kg/day calorie will be delivered until the oral feeding starts. However, between groups A and B only the amount of calories administered will be different. Patients will receive the same amount of fluid and ions during EN (see below).

**Ingredients of enteral tube feed: High Energy Enteral Tube Feed (100ml):**

**Energy:** 150 kcal (630 KJ), **Protein** 6g (16%E), **Carbohydrate:** 18.3g (49%E), **Fat:** 5.8g (35%E) + **Minerals:** 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 100mg Chloride (0%E). In this study we will use Nutrison Energy (Numil Ltd, Budapest, Hungary), which is a registered product in Hungary (reg. number: 1217).

**Zero Energy Enteral Tube Feed (100ml):**

**Energy:** 0 kcal (0 KJ), **Protein** 0g, **Carbohydrate:** 0g, Fat: 0g + **Minerals:** 134mg Sodium, 201mg Potassium, 108mg Calcium, 108mg Phosphorus, 34mg Magnesium, 5.562g Chloride (0%E) (in this study the local institutional pharmacy will provide it in accordance with the Hungarian regulations). Whenever 10 or 20 kcal/kg/day calories will be delivered, the mixture of the above-mentioned two solutions will be used.

**Type of enteral tube:** Patients neither vomiting nor having gastric fluid retention >250 ml will receive primarily NG tube. Patients either vomiting or having gastric fluid retention >250 ml will receive NJ tube (placement will be done either endoscopically or radiologically). In case of GCS 14 or lower in a patient who is not intubated, NG tube will be replaced by NJ tube (risk of aspiration). Abdominal X-ray will be used to check the tube's position.

1  
2 **Start of mixed feeding** (around 2620 kcal): Mixed feeding (1000 ml tap water distributed for 24 h  
3 and 300 g (around 1900 kcal) biscuits/toasts/low fat meal (at least 75% CHO containing ones)  
4 orally plus enteral tube feed (480ml, 720 kcal/day) will be started on the day when: (1) abdominal  
5 pain has been ceased for at least 6 h before the new day started, (2) CRP level has started  
6 decreasing and (3) amylase or lipase level has started decreasing  
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12 **Start of total feeding** (around 2000kcal): If the patients have no symptoms during the mixed  
13 oral/enteral feeding and the CRP, amylase or lipase levels are not rising again. Total feeding  
14 (according to local policy) can be started.  
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18 **Other issues:** The speed of EN will be different for the patients (depends on the body weight),  
19 however, the maximum speed of EN cannot exceed 65ml/h. In case of difficulties reaching the 30  
20 kcal/kg/day calories intake (if the patient's body weight is above 75 kg) additional intravenous  
21 calorie will be added using Sterofundin G. Maximum of 2000 ml (= 400 kcal) can be delivered in  
22 this way. If NG feeding is not tolerated, NG tube will be replaced to NJ tube as described above. If  
23 NJ feeding is not tolerated, EN will be reduced by 50% and increased again gradually until  
24 tolerated. If the re-increasing process is still not tolerated total parenteral nutrition (TPN) will be  
25 started to reach the required energy target. In case of SAP, TPN has to be delivered via central  
26 venous catheter.  
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## 42 **7. Other treatment of subjects**

43 General treatment indicated by the IAP/APA guideline will be utilized[53].  
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## 48 **8. Discharge of patients**

49 Uniformization of the length of hospital stay is necessary to avoid bias concerning LOH. Re-  
50 admission within one week after discharge has to be considered as the same hospital admission.  
51 Patients has to be counted as discharged from hospital/from the study when (1) oral feeding was  
52 tolerated for 24h, (2) no amylase/lipase level are elevated after total enteral feeding, (3) CRP level  
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1 is less than 50 mg/L, (4) abdominal pain has completely resolved (5) no other pancreatitis-related  
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4 complication requiring hospitalization is detected.  
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## 8 **9. Endpoints**

10 The following primary endpoints will be calculated: A combination of MOF more than 48h and  
11 Mortality. The following secondary endpoints will be analyzed: (1) pancreatic necrosis, (2)  
12 nutrition related complications: diarrhoea, aspiration pneumonia, pneumothorax due to central TPN  
13 catheter placement, (3) need for conversion from NG to NJ feeding tube (4) need for conversion  
14 from EN to TPN, (5) days until the start of total feeding, (6) use of antibiotics, (7) pain relapse, (8)  
15 CRP, (9) WBC, (10) PCT, (11) infection, (12) length of hospital stay, (13) need for ICU admission,  
16 (14) length of ICU therapy, (15) organ failure, (16) complications, (17) costs calculation. Notably,  
17 only direct costs will be calculated that include all medications, services, salaries of healthcare  
18 professionals, equipment and day care costs.  
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## 32 **10. Monitored parameters during hospitalization**

33 There will be a large variety of parameters monitored during the study (e.g. medical history,  
34 physical examination, laboratory tests, diagnostic imaging, therapy, interventions). Form A will  
35 contain the parameters collected on admission (Supplementary figure 1). Form B will contain  
36 parameters collected every day during hospitalization (Supplementary figure 2). Form C will  
37 contain parameters collected 1 month after hospital discharge (Supplementary figure 3). For details  
38 see supplementary materials or web page (<http://www.pancreas.hu/en/studies/goulash>), which will  
39 be available from February 2017. Data collection on the case report form (CRF) will be done  
40 electronically (see data management).  
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## 55 **11. Data management and statistical analyses**

56 **Data handling:** Data will be handled by IDMB. Electronic CRF (eCRF) will be used. The  
57 Investigator will ensure that the data in the eCRF are accurate, complete and legible. Detailed data  
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1 flow will be described in Data Management Plan (DMP). Data from completed eCRFs will be  
2 validated under the direction of the Data Manager at IDMB according to Data Cleaning Plan  
3 (DCP). Any missing, implausible, or inconsistent recordings in the eCRFs will be referred back to  
4 the Investigator using a data query form (DQF), and be documented for each individual subject  
5 before clean file status is declared. All changes to eCRF will be recorded. Before Data Base Lock  
6 Data Review Meeting will decide and document necessary steps related to any issue in the database  
7 and define the analysis sets. Member of the data review meeting are delegated investigator,  
8 biostatistician and data manager. Adverse events (AEs) will be coded using MedDRA. AdWare  
9 Research Ltd., who will act as IDMB, works according to GCP, GLP, FDA 21CFR PART11 and  
10 other relevant regulatory requirements. AdWare Ltd. has GLP and ISO 9001 certificates.  
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### 26 **Study populations:**

27 Three analysis populations will be defined:

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30 Safety Analysis Set (SAS): all patients enrolled in the study.  
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32 Per Protocol Set (PPS): all enrolled patients who finished the study conforming to the  
33 requirements of the Study Protocol.  
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36 Intention to Treat (ITT) all randomized participants who start on a treatment, excluding  
37 consent withdrawals.  
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43 **Withdrawal of a subject from PPS:** Any participants/investigators and IDMB can submit  
44 recommendation for dropouts from the PPS group with reasons given to SC. All recommendations  
45 will be filed. SC will discuss all the information and if the alteration in the protocol would be  
46 expected to have any bearing on the interventions and outcomes of the study, the patient will not be  
47 included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be  
48 ordered if: (1) any of the exclusion criteria diagnosed during the course of AP, (2) at least 50% of  
49 the energy requirement is not achieved on any days during the study, (3) parameters required for  
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2 answering the primary endpoints are missing or (4) serious medical reasons not related to  
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4 pancreatitis (i.e. accidents, stroke) occur.  
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8 **Applied softwares:** Statistical analysis will be performed using SAS 9.2 or SPSS 19 (or later)  
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10 statistical packages; Microsoft MSWord will be used for reporting.  
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14 **Statistical Methods:** Baseline patient and disease characteristics will be analyzed by using  
15  
16 descriptive analysis. Demographic and baseline characteristics will be summarized for the overall  
17  
18 study population. Continuous variables will be described by mean, median, standard deviation, and  
19  
20 ranges and categorical variables will be described by absolute and relative frequencies. A graphical  
21  
22 presentation of efficacy variables will be prepared, if applicable. Descriptive statistics for both of  
23  
24 the primary and secondary parameters will be analyzed similarly. Mean changes (and their 95% CI)  
25  
26 from baseline to end-of-study visit will be presented as well. Chi-squared tests will be applied to  
27  
28 compare proportions between the different groups. Mortality/extended MOF will be investigated  
29  
30 using the Kaplan-Meier analysis method; while subgroup comparisons will be performed using the  
31  
32 Chi-squared or Fisher's exact test, as appropriate. For safety data, descriptive statistics and  
33  
34 individual listings of adverse events will be also presented.  
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41 **Subgroups:** The following subgroups will be made during statistical analyses: (1) ages (under 40y,  
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43 40y-59y, 60y-80y), (2) BMI (below 20, 20-24, 25-29, 30-35, above 35), (3) the start of abdominal  
44  
45 pain before admission ( $\leq 24$ h, 24-48h,  $\geq 48$ h), (4) severity of the disease SAP and MAP. All  
46  
47 subgroup analyses, (5) etiologies will be done descriptively. No confirmatory statistical testing will  
48  
49 be applied. Hence, statistical tests and the p-values attached to them will be regarded as descriptive  
50  
51 and not as tests of hypotheses.  
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54 Details of the applied statistical tests will be described in the Statistical Analysis Plan.  
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## 12. Early quality assessment.

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Early quality assessment check will be performed on the first 100 patients. IDMB (AdWare Ltd.) will perform an independent assessment of the trial related documents and activities, with the aim of ensuring the respect of subject's right, safety and well-being and to guarantee the plausibility of clinical data. The similarity of groups at baseline will be also checked. IDMB will report to SC. SC will discuss all the information and if the differences would be expected to have any bearing on the interventions and outcomes of the study or the overall dropout rate from PPS is above 20 percent of all participants who were randomized or allocated into each group or the differential dropout rate is above 15 percent between the arms, the study needs to be reassessed and IDMB will make recommendations regarding either reevaluation of power calculation, extension of recruitment period, extension of number of study centers or termination of trial.

### 13. Interim analyses and premature termination of the study.

IDMB can also recommend to stop the trial early for ethical reasons if one of the groups clearly shows evidence of a significant benefit. An interim analysis will be performed on the primary endpoint when 50% of patients have been randomized and discharged from the hospital. The interim analysis will be performed by the IDMB. IDMB will report to SC.

The Haybittle–Peto boundary approach will be used. If the interim analysis shows a probability of equal to, or less than 0.001 that a difference as extreme between the treatments is found, given that the null hypothesis is true, then the trial will be stopped early.

### 14. Centres

The trial will start in two centres (University of Debrecen and University of Pécs), after which the study is open for other centres. In all cases IDMB will make an audit of the centre and will report to the SC. SC keeps the right to decide whether the centre meets the required quality to join the study. Compulsory requirements for a centres: (1) it needs to treat at least 50 AP patients a year, (2) it needs to have all the equipment required for the study, (3) besides the regular medical team the

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2 centre has to appoint at least one doctor and one nurse/administrator fully available for the trial with  
3  
4 no additional commitments which can interfere with her/his duty when her/his availability is  
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6 required, (4) the blinding described above can be fully utilized, (5) all persons need to attend a  
7  
8 preliminary meeting where all the details concerning the studies are discussed fully and have  
9  
10 qualified as investigators in a GCP course. Centres wish to join need to send a letter of intent to the  
11  
12 corresponding author by e-mail.  
13

### 14 15 16 17 **15. Publication policy**

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19 Centres providing more than 25 patients can provide two authors to the authorship list. Every  
20  
21 additional 25 patients will give the opportunity to nominate an additional author.  
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### 24 25 26 **16. Feasibility**

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28 As a general protocol for the treatment of AP at the Centre for Translational Medicine at the  
29  
30 University of Pécs, patients suffering from AP receive early EN (using nasogastric tube). Patients  
31  
32 receive 50 ml Nutrison Energy per hour starting immediately when they arrive to the ward from the  
33  
34 Emergency Department. Patients data between the period of 1 January – 31 May 2016 were  
35  
36 analyzed and the following observations were noted: (1) In 85% of all AP admission early EN  
37  
38 could have been started within 24 h. In 15% of the cases it was not achievable due to the delayed  
39  
40 transfer of the patients to the ward or vomiting. In these cases patients received NG tube later or  
41  
42 they received NJ tube whenever X-ray assistance was available. (2) around 80% of NG-fed patients  
43  
44 tolerated NG feeding without any complications. The rest of the patients who had gastric retention  
45  
46 or vomiting NG feeding was stopped and they received NJ tube whenever X-ray assistance was  
47  
48 available. (3) Comparing the outcome (rate of severity, mortality, necrosis, intervention, etc.) of this  
49  
50 treatment protocol with the nil per os protocol utilized in most of the Hungarian hospitals revealed  
51  
52 that patients enjoy benefits with no risk of early enteral feeding which data confirm the literature  
53  
54 data described in the introduction. Concerning the number of patients at the University of Pécs  
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2 around 250 and at the University of Debrecen around 150 patients are admitted annually. Therefore,  
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4 if no other Institution would join the study it can be completed within 3 years.  
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### 8 9 **17. Safety**

10 Since no unknown drugs/therapy are used in the study no adverse and serious adverse events (SAE)  
11 are expected/interpretable that would be attributable to the intervention during the trial. In this trial  
12 IDMB will examine safety variables after every 16 patients have completed. Moreover,  
13 investigators will report AE or SAE via a separate form which has to be sent to IDMB and SC. SC  
14 will discuss and if the adverse effect is confirmed it will be reported to the relevant institutional and  
15 national ethical committee <http://www.ett.hu/tukeb.htm>.  
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### 26 27 **18. Additional information and future plan.**

28 Blood samples (serum and plasma) will be stored from all patients in order to study laboratory  
29 parameters later if required (e.g. the laboratory could not measure it), and in order to build up a  
30 biobank for later clinical studies to which all participants will be given informed consent. The  
31 samples will be stored on -80°C. A follow-up study (called GOULASH PLUS) is under preparation  
32 in order to follow the patients for up to 5 years after the study. The study protocol will also be  
33 published.  
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## 43 44 **DISCUSSION**

45 Here we report the protocol of a prospective double-blind RCT to study the effects of early energy  
46 restoration in AP. The pre-clinical studies [1, 9] and meta-analyses suggest that early energy  
47 supplementation should be beneficial. Our main hypothesis is that elevating the energy level of  
48 acinar and ductal cells will prevent these cells from injury, therefore, it will decrease the extent of  
49 necrosis during AP. Since both the local and systemic complications (immune response) largely  
50 depend on the extent of the necrosis we propose that this intervention will reduce multi-organ  
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1 failure and mortality in AP as well. Although nutritional interventions for patients with mild  
2 pancreatitis are probably not needed, we must involve all AP patients into the study. It has to be  
3 highlighted that the main aim of the study is not to find new treatments in MAP or SAP, but to  
4 prevent the development of SAP. This is the reason why severity cannot be a selection criteria but  
5 has to be the primary endpoint. Concerning ethical issues, this study has very low risk for patients.  
6 The enteral solution (Nutrison Energy) used in this study is widely used in several diseases related  
7 malnutrition in patients and has almost no contraindications, therefore no adverse events are  
8 expected during the trial.  
9

## 10 11 12 13 14 15 16 17 18 19 20 21 22 **ETHICS AND DISSEMINATION**

23 The trial is registered at the ISRCTN registry (ISRCTN63827758) and got the relevant ethical  
24 approval with the reference number of 55961-2/2016/EKU issued by The Scientific and Research  
25 Ethics Committee of the Medical Research Council. It is almost needless to say that at the end of  
26 the project we will disseminate our results in the medical community. We will publish our results in  
27 an open access way.  
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## 37 **CONCLUSION**

38 This study provides the first and type A evidence concerning the necessity of energy intake for  
39 patients suffering from AP.  
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43 This protocol is the first version of the trial completed on 24<sup>th</sup> May 2017.  
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## 48 **List of abbreviations**

49 AE – adverse event

50 AP – acute pancreatitis

51 BMI – body mass index

52 CRF – case report file  
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1 CRP – C-reactive Protein

2 DCP – data cleaning plan

3 DMP – data management plan

4 DQF – data query form

5 eCRF – electronic clinical report form

6 EN – enteral nutrition

7 GOULASH – name of the study: general utilization of early energy administration in acute  
8 pancreatitis.

9 HPSG – Hungarian Pancreatic Study Group

10 ICU – intensive care unit

11 IDMB – Independent data management and biostatistics provider company

12 ITAB – International Translational Advisory Board

13 ITT – Intention to Treat

14 LOH – length of hospital stay/hospitalization

15 MAP – mild and moderate AP

16 MOF – multi organ failure

17 NG – nasogastric

18 NJ – nasojejunal

19 PCT – procalcitonin

20 PN – parenteral nutrition

21 PPS – Per Protocol Set

22 SAE – severe adverse event

23 SAS – Safety Analysis Set

24 SAP – severe AP

25 SC – Steering Committee

26 TPN – total parenteral nutrition

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2 WBC – white blood cell count  
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6 **Availability of data and materials**  
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8 Not applicable, because the trial has not completed patient recruitment.  
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12 **Competing interest**  
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14 The authors declare that they have no competing interests.  
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19 **Funding**  
20

21 Centre costs (IT, biostatistics, trial organization, etc) are covered by the University of Pécs,  
22 Momentum Grant of the Hungarian Academy of Sciences (LP2014-10/2014); and Economic  
23 Development and Innovation Operative Programme Grant and Highly Cited Publication Grant of  
24 the National Research, Development and Innovation Office (GINOP-2.3.2-15-2016-00015, KH-  
25 125678). Since no additional treatment is necessary for the study, the general healthcare costs are  
26 covered by the National Healthcare System.  
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37 **Authors' contributions**  
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39 All authors were involved in the study design, edited the manuscript, read and approved the final  
40 manuscript. During the study KM, ANS, DP and PV are going to randomize the patients, obtain the  
41 consent form and ensure the blinding. AM, KS, JB, SG, MP, PS, ZV and TT are going to manage  
42 the treatment of the patients. ÁV will be responsible for the organization, quality and timing of the  
43 endoscopic treatments, ZM and RH for the intensive care, NF and IB for the imaging and  
44 interventional radiology, DK and RP for the surgical treatment if needed. PAV and EL will prepare  
45 the nutritional solutions. ML, JN, MST and OP are members of ITAB. TM and AS will be members  
46 of SC. PH and KM drafted the manuscript.  
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### 10 **Figure legends**

11  
12 Fig. 1 shows the flow chart of participants according to SPIRIT 2013 statement [52].

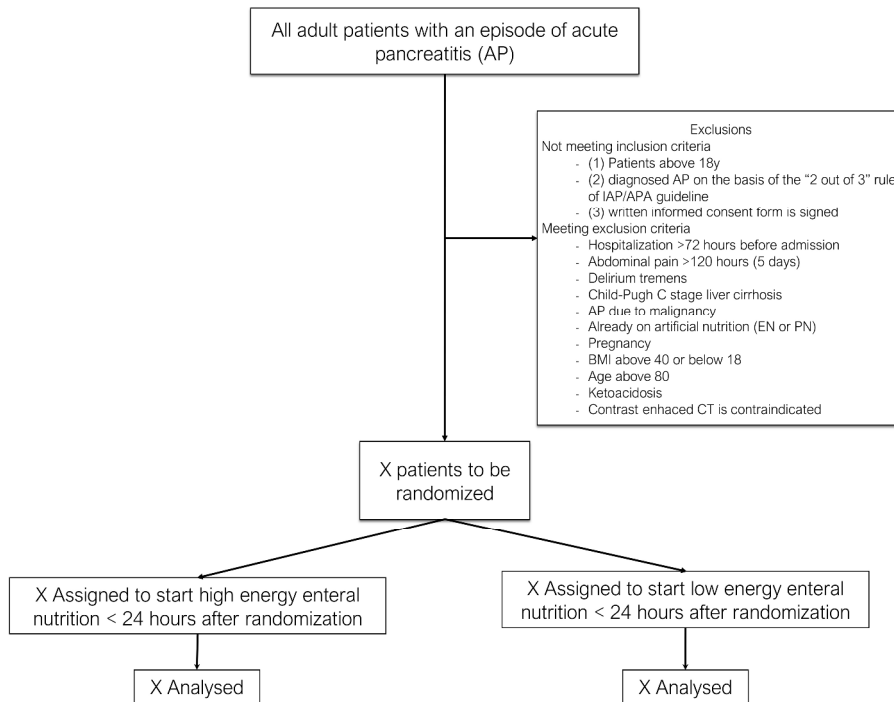
13  
14 Fig. 2 shows the schedule of enrolment, interventions, and assessments according to SPIRIT 2013  
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16 statement [52]. Patients will be randomized to group A (high energy) or B (low energy).  
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21 Suppl. Fig. 1 Form A contains the parameters collected on admission.

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23 Suppl. Fig. 2 Form B contains parameters collected every day during hospitalization.

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26 Suppl. Fig. 3 Form C contains parameters collected 1 month after hospital discharge.  
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Flow of participants

361x270mm (300 x 300 DPI)

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TIMEPOINT**	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
	<24h	0	day1	day2	day3	dayx	discharge	1m after discharge
<b>ENROLMENT:</b>								
Eligibility screen	X							
Informed consent	X							
Laboratory test	X							
CT examination	X							
Allocation		X						
<b>INTERVENTIONS:</b>								
High energy administration			←————→					
Low energy administration			←————→					
<b>ASSESSMENTS:</b>								
Questionnaire A		X						
Questionnaire B			X	X	X	X	X	
Questionnaire C								X

Intervention. Patients will be randomized to group A (high energy) or B (low energy)

194x169mm (300 x 300 DPI)

only

**FORM-A****Acute  
Pancreatitis****GOULASH**

**The physical examination has to be done ON ADMISSION!**  
**The blood for laboratory parameters has to be drawn ON ADMISSION!**  
**This form has to be filled ON ADMISSION!**

**Questionnaire****1. Patient personal details**

Insurance number:.....  
 First name:.....  
 Last name: .....,  
 Date of birth:.....  
 Gender: female male  
 Ethnicity/Race: White / Black / Asian-Indian Not known

**2. Details from the medical history**

**Alcohol consumption:** yes / no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/day):.....  
 since when? (years):.....  
 Alcohol consumption in the last 2 weeks: .....,  
 if not:  
 Did you drink alcohol earlier? yes/no  
 if yes: frequency: occasionally/monthly/weekly/daily  
 amount (g/occasion):.....  
 For how many years?.....  
 How long ago did you stop drinking alcohol?.....

*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

**Smoking:** yes / no  
 if yes: amount (cigarettes/day):.....  
 For how many years? .....,  
 if not:  
 Did you smoke earlier? yes/no  
 if yes: amount (pcs/occasion):.....  
 For how many years?.....  
 How long ago did you stop smoking? .....,

**Drug abuse:** yes / no *Prescribed medication should not be included here.*  
 if yes: type of drug:..... amount:.....  
 since when (year):.....  
 (if there are more drugs, please describe them in the NOTES section at the end)

**Diabetes mellitus:** yes / no  
 if yes: type: Type I. / Type II./Type III. c / MODY  
 since when (year):.....

Country:

Town:

Hospital:

Doctor:

Patient No:

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FORM-A

Acute Pancreatitis

GOULASH

**Lipid metabolism disorder:** yes / no  
 if yes: type: ..... since when (year):.....

**Any disease of the pancreas:** yes / no *Not counting the current episode.*  
 if yes: acute pancreatitis/ chronic pancreatitis/ autoimmune pancreatitis/ tumor/ other  
 if other: please describe:.....

If the patient had ACUTE PANCREATITIS in the history:  
 How many times did the patient have acute episodes before this episode:.....  
 When did the patient have the first acute episode (year):.....

If the patient has CHRONIC/AUTOIMMUNE PANCREATITIS:  
 When was it diagnosed?.....  
 How many times did the patient have acute episodes before this episode:.....  
 When did the patient have the first acute episode (year):.....

If the patient has PANCREATIC CANCER::  
 When was it diagnosed?.....  
 Was the patient diagnosed with chronic pancreatitis? yes / no  
 If yes, when was it diagnosed?.....  
 How many times did the patient have acute episodes before this episode?:.....  
 When did the patient have the first acute episode (year):.....

Other information:  
 .....

**Pancreas disorders in family history:**  
 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:.....  
 .....

**Congenital Anatomical Malformation of the pancreas:** yes / no / no data  
 if yes: please describe:.....

**Other illnesses:** yes / no  
 if yes: please list/describe them:.....

**Medications taken regularly:** yes / no *Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)*

if yes:  
 name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
 if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
 type of administration:.....other notes: .....

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**FORM-A****Acute  
Pancreatitis****GOULASH**

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

**Diet:** yes / no  
if yes: please describe:.....

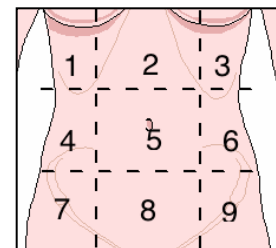
**3. Etiology** *The answer is "yes" if the etiological factor is proved, the answer is "no" if the etiological factor can be ruled out, the answer is "no data" if the etiological factor was not examined. Please answer "yes" to "Idiopathic" if etiological factor was not identified.*

Biliary	yes	no	no data
Alcohol	yes	no	no data
Virus infection	yes	no	no data
Trauma	yes	no	no data
Drug-induced	yes	no	no data
Congenital anatomical malformation	yes	no	no data
Cystic fibrosis	yes	no	no data
Gluten-sensitive enteropathy	yes	no	no data
Hypertriglyceridaemia	yes	no	no data
Genetic	yes	no	has not been tested yet
Idiopathic	yes	no	
Other	yes	no	

if yes: please describe:.....

**4. Complains, symptoms**

**Abdominal pain:** yes / no  
if yes: since when (hours):.....  
type: cramping / dull / sharp  
intensity (1-10):.....  
location: diffuse / localized  
Please mark the location!  
radiation:.....



**Nausea:** yes / no

**Vomiting:** yes / no  
if yes: how many times:.....  
contents of cast:.....

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# Acute

# FORM-A

# Pancreatitis

# GOULASH

**Subfebrility/fever:** yes / no  
 if yes: since when:.....  
 degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no  
 if yes: how much (kg):.....  
 How long did it take? (weeks):.....

**Jaundice:** yes / no  
 if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus  
*Please refer to the period just before your symptoms has started.*

## 5. Admission details and state

**Blood pressure (Hgmm):**..... **Heart rate (/minute):**.....  
**Body weight (kg):**..... **Body height (cm):**.....  
**Respiratory rate (/minute):**..... **Body temperature (°C):** .....  
 axillary/rectal

**Oxygen saturation (%):** ..... Previous O2 therapy: yes/no

**Abdominal tenderness :** yes / no **Abdominal guarding:** yes / no

**Jaundice:** yes / no

**Glasgow Coma Scale (GCS):**.....

### Glasgow Coma Scale:

#### Eye response

4 points: Spontaneous eye opening  
 3 points: Eye opening in response any speech  
 2 points: Opening to response to pain  
 1 point: No eye opening

#### Verbal Response

5 points: Orientated  
 4 points: Confused conversation  
 3 points: Inappropriate speech  
 2 points: Incomprehensible speech  
 1 point: No verbal response.

#### Motor Response

6 points: Obeying command  
 5 points: Localizing response to pain  
 4 points: Withdraws to pain  
 3 points: Decorticate posture  
 2 points: Decerebrate posture  
 1 point: No response to pain

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**FORM-A****Acute  
Pancreatitis****GOULASH****6. Laboratory parameters on admission****OBLIGATORY PARAMETERS:**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
Serum glucose (mmol/l)	
Hemoglobin A1C (%)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
C-reactive protein (mg/l)	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	

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# Acute

# FORM-A

# Pancreatitis

# GOULASH

**OTHER PARAMETERS (if measured):**

IgA (g/l)	
IgM (g/l)	
IgG (g/l)	
IgG4 (g/l)	
CA 19-9 (U/ml)	
PaO <sub>2</sub> (Hgmm)	
HCO <sub>3</sub> (mmol/l)	
sO <sub>2</sub> (%)	
sweat chloride (mmol/l)	
urine amylase	
urine lipase	
urine creatinine	
(other)	

Virus serology: yes / no Which viruses? ..... results:.....

**7. Imaging examinations on admission**

Does the patient have pleural fluid? yes    no    N/A

Does the patient have lung infiltrate? yes    no    N/A

Does the patient have abnormal pancreatic structure? yes    no    N/A

If yes: hypoechoic/hyperechoic/peripancreatic fluid/irregular and blurred contours/Wirsung dilatation (above 1mm)/ascites/calcification/cyst

**Abdominal X-ray:** yes                      no  
 Description:  
 .....  
 .....

**Chest X-ray:** yes                      no  
 Description:  
 .....  
 .....

**Chest Computed Tomography:** yes                      no  
 Description:  
 .....  
 .....

**Abdominal Computed Tomography:**  
 Modified CTSI Score: .....0-10.....  
*Please NOTE! Abdominal CT is compulsory on admission*

**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

THE RCT IS ORGANIZED BY THE HUNGARIAN PANCREATIC STUDY GROUP



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 Kata Márta **Tel:** +36 20 211 5868 **e-mail:** k.marta@tm-pte.org

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**FORM-A****Acute  
Pancreatitis****GOULASH**- **CTSI:****I. Pancreas**

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

**III. Extrapancreatic findings**

- presence of extrapancreatic findings

**DETAILED REPORT**- **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 (nonenhancement):**

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60%, above 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

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# Acute

# Pancreatitis

# GOULASH

# FORM-A

**12. Epicrisis** *A short summary of the hospitalization (how the patient got to medical care, diagnosis, most important facts and events of the hospitalization, what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
.....

### NOTES

.....  
.....

### DATE:

YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

THE TOTAL TIME SPENT THE PATIENT ON ADMISSION:            HOUR ..... MIN: .....

**NAME OF THE DOCTOR MADE THE RANDOMIZATION:** ..... **SIGNATURE:** .....

*Please NOTE! The doctor made the randomization MUST NOT involved in the treatment of patients any longer. She/He has to keep the information secretly from the patients and medical team involved in the treatment.*

**NAME OF THE DOCTOR EXAMINED/TREATED THE PATIENT:** ..... **SIGNATURE:** .....

For peer review only

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**FORM-B****Acute  
Pancreatitis****GOULASH****PLEASE FILL IN EVERY DAY DURING THE HOSPITAL STAY****Day No:****Date** (+hour, min)**GOULASH No:**

(Automatically generated)

**1. Patient personal details**

First name:.....

Last name: .....

**2. Complains, symptoms****Abdominal pain:** yes / no

if yes: since when (hours):.....

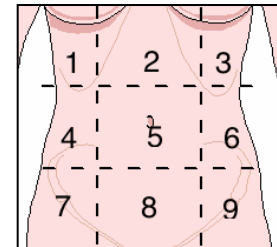
type: cramping / dull / sharp

intensity (1-10):.....

location: diffuse / localized

Please mark the location!

radiation:.....

**Nausea:** yes / no*If YES, retention measurement has to be performed.***Vomiting:** yes / no*If YES, NG tube has to be replaced by NJ tube.***Subfebrility/fever:** yes / no

if yes: since when:.....

degree (°C):.....

**Appetite:** good / retained / bad**Stool:** yes / no

if yes: normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

THE RCT IS ORGANIZED BY THE HUNGARIAN PANCREATIC STUDY

**HPSG chair and leader of the Steering Committee:**Péter Hegyi **Tel:** +36 70 375 1031 **e-mail:** p.hegyi@tm-pte.org**Principal Investigator:**Kata Márta **Tel:** +36 20 211 5868 **e-mail:** k.marta@tm-pte.org**7/24 HOT LINE****+36 30 292 5534. ☎61180**

# FORM-B

# Acute Pancreatitis

# GOULASH

### 3. Patient's state

Blood pressure (Hgmm):..... Heart rate (/minute):.....

Body weight (kg):.....

Respiratory rate (/minute):.....

Body temperature (°C): .....

axillary/rectal

Oxygen saturation (%): .....

O2 therapy: yes/no

Abdominal tenderness :        yes / no

Abdominal guarding:        yes / no

Jaundice:                        yes / no

Glasgow Coma Scale (GCS):.....

**Glasgow Coma Scale:**

**Eye response**

- 4 points: Spontaneous eye opening
- 3 points: Eye opening in response any speech
- 2 points: Opening to response to pain
- 1 point: No eye opening

**Motor Response**

- 6 points: Obeying command
- 5 points: Localizing response to pain
- 4 points: Withdraws to pain
- 3 points: Decorticate posture
- 2 points: Decerebrate posture
- 1 point: No response to pain

**Verbal Response**

- 5 points: Orientated
- 4 points: Confused conversation
- 3 points: Inappropriate speech
- 2 points: Incomprehensible speech
- 1 point: No verbal response.

### 4. Laboratory parameters

**OBLIGATORY PARAMETERS**

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

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**FORM-B****Acute  
Pancreatitis****GOULASH****OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	
Procalcitonin (ng/ml)	
IgA (g/l)	
IgM (g/l)	
IgG (g/l)	
IgG4 (g/l)	
CA 19-9 (U/ml)	
PaO <sub>2</sub> (Hgmm)	
HCO <sub>3</sub> (mmol/l)	
sO <sub>2</sub> (%)	
sweat chloride (mmol/l)	
urine amylase	
urine lipase	
urine creatinine	
(other)	

**Blood glucose (by finger stick test)** *Compulsory on the first day:*

4h	mmol/l	amount of insulin if administered : ..... IU
8h	mmol/l	
12h	mmol/l	
16h	mmol/l	
20h	mmol/l	
24h	mmol/l	

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3



HPSG

www.pancreas.hu

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# FORM-B

# Acute Pancreatitis

# GOULASH

## 5. Imaging (if performed)

yes no

### Abdominal ultrasonography:

yes no

*2 hours before the examination the enteral feeding has to be stopped. The amount of enteral feeding which was not given have to be administered additionally to the normal feeding in the next 10h. (for example: If the patient receive 45 ml/h and 90ml was not given due to the examination, the patient has to receive 54ml (45ml + 9ml) for the forthcoming 10h.*

- **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:

.....  
 .....

### Abdominal X-ray:

yes no

Description:

.....  
 .....

### Chest X-ray:

yes no

Description:

.....  
 .....

### Chest Computed Tomography:

yes no

Description:

.....  
 .....

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## FORM-B

Acute  
Pancreatitis

## GOULASH

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:

## I. Pancreas

- Normal pancreas
- Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

## II. Size of Necrosis

- Necrosis absent
- < 30% necrosis
- > 30% necrosis
- > 60% necrosis

## III. Extrapancreatic findings

- presence of extrapancreatic findings
- 

## DETAILED REPORT

## - 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 (nonenhancement):

- Largest diameter of necrosis area: ..... cm
- Location of necrosis: .....
- Type: patchy / full width
- Estimated necrosis: 0% , < 30% , 30% - 60%, above 60%

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

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# FORM-B

# Acute Pancreatitis

# GOULASH

- Distant **abdominal fluid**:
  - o Small amount (hard to see, less than 2 cm in lesser pelvis, less than 1 cm around liver/spleen)
  - o Moderate amount (easy to see, but without pelvic or abdominal distension)
  - o Large amount with abdominal/pelvic distension
  
- **Pleural effusion**:
  - o none
  - o one sided:..... (AP diameter: ..... cm)
  - o Both sides, L - ..... cm, R - ..... cm
  
- **Extrapancreatic findings**:
  - o Inflammation (Cholecystitis, Duodenitis, etc.) location: .....
  - o Cholecystolithiasis
  - o Choledocholithiasis
  - o Signs of bowel ischaemia
  - o Bowel distension, ileus
  - o Venous thrombosis
  - o Pseudoaneurysm
  - o Parenchymal organ involvement, define: .....

Other Description:

.....

.....

## 6. Microbiology examination

Biological sample collection                      yes                      no

If yes:                      place: /blood, urine, airway, pancreas, other/

result:                      .....

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# Acute

# FORM-B

# Pancreatitis

# GOULASH

**Pain management:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Antibiotic therapy:**    yes    no

if yes:

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....

if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)

type of administration:.....other notes: .....

**Insulin:**                    yes    no

if yes,

name of the medication:.....

dosage:.....

**Intensive care:**        yes    no

if yes,

namely (ventilation, vasopressor therapy):.....

**Other:**

if yes,

please describe:.....

.....

.....

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# FORM-B

# Acute Pancreatitis



### 8. Interventions, endoscopic treatment:

yes no

if yes: ERCP-EST/endobiliary stent/Wirsung stent/cysta drainage  
 Stent: 1 plastic stent/more plastic stents/uncovered metal stent/covered metal stent  
 Early complications: none/bleeding/perforation

ERCP: yes no

if yes:

Successful biliary cannulation: yes no if yes: notes: .....  
 Precut: yes no if yes: needleknife/precut papillotomy  
 EST: yes no if yes: biliary/pancreatic  
 Stone extraction: yes no  
 Stent: yes no if yes: metal/plastic  
 How many pcs? diameter(Fr)? length(cm)?  
 Pancreatic duct filling: yes no if yes: notes: .....

### 9. Complications

Pancreatic: yes no no data  
 if yes, fluid collections / pseudocyst / necrosis / diabetes  
 Organ failure: yes no  
 if yes, lung / heart / kidney /other  
 Duration of organ failure: <48 hours >48 hours  
 Death: yes no  
 if yes: the exact time of death: ..... e.g. 10.25 or 22.45

### NOTES

.....  
.....  
.....

### DATE:

YEAR: ..... MONTH: ..... DAY: .....

NAME OF THE DOCTOR: .....SIGNATURE: .....

NAME OF THE NURSE: .....SIGNATURE: .....

NAME OF THE SCIENCE ADMINISTRATOR: .....SIGNATURE: .....

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FORM-C

Acute  
Pancreatitis

GOULASH

Questionnaire

1. Patient personal details

First name:.....

Last name: .....

GOULASH No:

(Automatically generated)

2. Details from the medical history (in the last month)

Alcohol consumption: yes / no  
if yes: frequency: occasionally/monthly/weekly/daily  
amount (g/day):.....

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

Smoking: yes / no  
if yes: amount (cigarettes/day):.....

Drug abuse: yes / no Prescribed medication should not be included here.  
if yes: type of drug:..... amount:.....  
(if there are more drugs, please describe them in the NOTES section at the end)

Any re-hospitalization?: yes / no  
if yes: cholecystectomy: yes no  
recurrent AP: yes no  
other: .....

Medications taken regularly in the last month: yes / no  
Please specify the name of the active substance (e.g. "acetylsalicylic acid"). Please specify the amount using the International System of Units –SI (e.g. milligram, gram)  
if yes:  
name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....

name:.....active substance:.....dose(gram,milligram, etc.).....  
if fluid, concentration (e.g. 10%, 1g/2ml, etc.).....how many times per day (e.g. 3)  
type of administration:.....other notes: .....



# FORM-C

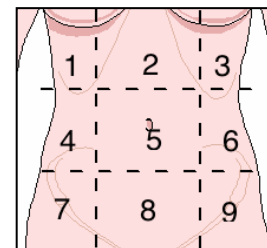
# Acute Pancreatitis

# GOULASH

**Diet:** yes / no  
 if yes: please describe:.....

### 3. Complains, symptoms

**Abdominal pain:** yes / no  
 if yes: since when (hours):.....  
 type: cramping / dull / sharp  
 intensity (1-10):.....  
 location: diffuse / localized  
 Please mark the location!  
 radiation:.....



**Nausea:** yes / no

**Vomiting:** yes / no  
 if yes: how many times:.....  
 contents of cast:.....

**Subfebrility/fever:** yes / no  
 if yes: since when:.....  
 degree (°C):.....

**Appetite:** good / retained / bad

**Weight loss:** yes / no  
 if yes: how much (kg):.....  
 How long did it take? (weeks):.....

**Jaundice:** yes / no  
 if yes: for how long:.....

**Stool:** normal / diarrhea / constipation / fatty / putrid / undigested food/bloody/mucus

### 4. Laboratory parameters

#### OBLIGATORY PARAMETERS

Amylase (U/l)	
Lipase (U/l)	
White blood cell (WBC) count (G/l)	
Red blood cell (RBC) count (T/l)	
Hemoglobin (g/l)	
Hematocrit (%)	
Thrombocyte (G/l)	
C-reactive protein (mg/l)	

**OTHER PARAMETERS (if measured):**

Serum glucose (mmol/l)	
Blood urea nitrogen (mmol/l)	
Creatinine (umol/l)	
eGFR	
ASAT/GOT (U/l)	
Lactate dehydrogenase LDH (U/l)	
Calcium (mmol/l)	
Sodium (mmol/l)	
Potassium (mmol/l)	
Total protein (g/l)	
Albumin (g/l)	
Cholesterol (mmol/l)	
Triglyceride (mmol/l)	
ALAT/GPT (U/l)	
Gamma GT (U/l)	
Total bilirubin (umol/l)	
Direct/Conjugated bilirubin (umol/l)	
Alkaline phosphatase (U/l)	

**5. Imaging examination**

**Abdominal ultrasonography:**                      yes                      no

Description:

**Ultrasound:**- **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)

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## FORM-C

Acute  
Pancreatitis

## GOULASH

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- Size of peripancreatic fluid or pseudocyst: ..... cm
  - **Pancreas homogeneity:**
    - o Homogenous
    - o Inhomogeneous, includes area(s) of low echogenicity
    - o Inhomogeneous, includes calcifications
  - In case of circumscribed low echogenicity area, it's size: ..... cm
  - **Wirsung** dilatation: YES / NO (yes, diameter: ..... mm)

Other Description:

.....

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**Abdominal Computed Tomography:**    yes                      no                      **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

Modified CTSI Score: .....0-10.....

*Please NOTE! Abdominal CT is compulsory if*

*- Abdominal ultrasonography is not fully completed OR*

*- There is any alteration on abdominal ultrasonography*

- **CTSI:**

**I. Pancreas**

- o Normal pancreas
- o Intrinsic pancreatic abnormalities with or without inflammatory changes in peripancreatic fat
- o pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis

**II. Size of Necrosis**

- o Necrosis absent
- o < 30% necrosis
- o > 30% necrosis
- o > 60% necrosis

**III. Extrapancreatic findings**

- o presence of extrapancreatic findings

**DETAILED REPORT**

- **Pancreas Size:**

- o Normal
- o Partially enlarged (body AP diameter is over 2 cm and/or head AP diameter is over 2,5 cm, none exceeds 3 cm)

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**FORM-C**

**Acute  
Pancreatitis**

**GOULASH**

- 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** (nonenhancement):
  - Largest diameter of necrosis area: ..... cm
  - Location of necrosis: .....
  - Type: patchy / full width
  - Estimated necrosis: 0% , < 30% , 30% - 60%, above 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
  - Choledocholithiasis
  - Signs of bowel ischaemia
  - Bowel distension, ileus
  - Venous thrombosis
  - Pseudoaneurysm
  - Parenchymal organ involvement, define: .....

Other Description:

.....  
 .....

# FORM-C

# Acute Pancreatitis



**6. Complications** *Please register pancreatic complication of fluid collection/pseudocyst/necrosis only if you had imaging proof on the day of admission, otherwise, please mark "no data".*

**Pancreatic:**                    yes                    no                    no data  
 if yes:                    fluid collections /pseudocyst / necrosis / diabetes

**Organ failure:**            yes                    no  
 if yes:,                    lung /heart / kidney /other

**Death:**                    yes                    no  
 If yes: the exact date of death: ..... e.g. 10.25 or 22.45

**7. Epicrisis** *A short summary (what happened with the patient after the hospitalization, any recommended control examinations, surgery).*

.....  
 .....

**DATE:**  
 YEAR: ..... MONTH: ..... DAY: ..... HOUR ..... MIN: .....

**NAME OF THE DOCTOR** : .....**SIGNATURE:** .....

For peer review only



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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	2,17_____
	2b	All items from the World Health Organization Trial Registration Data Set	17_____
Protocol version	3	Date and version identifier	17_____
Funding	4	Sources and types of financial, material, and other support	17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,18_____
	5b	Name and contact information for the trial sponsor	5_____
	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	5, 17_____
	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)	5, 12 13_____

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49**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, 4 15, 16_____
	6b	Explanation for choice of comparators	4_____
Objectives	7	Specific objectives or hypotheses	4_____
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)	4, 6_____

**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	13, 10_____
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)	6, 13_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8, 9_____
	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)	9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9_____
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	9, 10, 11, 14_____
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)	7, 10_____

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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_____
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6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6_____
7				

### 8 **Methods: Assignment of interventions (for controlled trials)**

#### 9 Allocation:

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12	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	6, 7_____
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18	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	7_____
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22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6, 18_____
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25	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7_____
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28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
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### 32 **Methods: Data collection, management, and analysis**

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34	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	10, 11, 12, 13, 14, 15__
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39		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, 10_____
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3	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	10_____
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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	11, 12, 13_____
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12, 13_____
11				
12		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)	10, 11, 12_____
13				
14				
15				
16	<b>Methods: Monitoring</b>			
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18	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	6, 10, 12_____
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23		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	13, 14_____
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26	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	14_____
27				
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14, 6, 10, 12_____
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33	<b>Ethics and dissemination</b>			
34				
35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 17_____
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38	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)	14_____
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, _____
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15 _____
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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	10 _____
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17 _____
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15	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	2 _____
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18	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	14 _____
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21	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	2 _____
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	13 _____
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2 _____
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30	<b>Appendices</b>			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____
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35	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	15 _____
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\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.