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The role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study

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7 2 idiopathic acute pancreatitis (PICUS): study protocol for a nationwide
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10 3 prospective cohort study
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53 66 List of abbreviations
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56 67 ALT = alanine aminotransferase
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59 68 BMI = body mass index
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3 69 CBD = common bile duct
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6 70 CI = confidence interval
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9 71 CRF = case report form
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12 72 CT = computed tomography
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15 73 ERCP = endoscopic retrograde cholangiopancreatography
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18 74 EUS = endoscopic ultrasonography
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21 75 IAP = idiopathic acute pancreatitis
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24 76 IPMN = intraductal papillary mucinous neoplasm
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27 77 IQR = interquartile range
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30 78 MRCP = magnetic resonance cholangiopancreatography
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33 79 MRI = magnetic resonance imaging
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2
3 87 **Abstract**
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5
6 88 **Introduction**
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8 89 Idiopathic acute pancreatitis (IAP) remains a dilemma for physicians as it is uncertain whether patients
9
10 90 with IAP may actually have an occult etiology. It is unclear to what extent additional diagnostic
11
12 91 modalities such as endoscopic ultrasonography (EUS) are warranted after a first episode of IAP in order
13
14 92 to uncover this etiology. Failure to timely determine treatable etiologies delays appropriate treatment
15
16 93 and might subsequently cause recurrence of acute pancreatitis. Therefore, the aim of the PICUS study
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18 94 is to determine the value of routine EUS in determining the etiology of pancreatitis in patients with a
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20 95 first episode of IAP.
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28 97 **Methods and analysis**
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30 98 PICUS is designed as a multicenter prospective cohort study of 106 patients with a first episode of IAP
31
32 99 after complete standard diagnostic work-up, in whom a diagnostic EUS will be performed. Standard
33
34 100 diagnostic work-up will include a complete personal and family history, laboratory tests including
35
36 101 serum alanine aminotransferase, calcium and triglyceride levels, and imaging by transabdominal
37
38 102 ultrasound, magnetic resonance imaging or magnetic resonance cholangiopancreatography after
39
40 103 clinical recovery from the acute pancreatitis episode. The primary outcome measure is detection of
41
42 104 etiology by EUS. Secondary outcome measures include pancreatitis recurrence rate, severity of
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44 105 recurrent pancreatitis, readmission, additional interventions, complications, length of hospital stay,
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46 106 quality of life, mortality and costs, during a follow-up period of 12 months.
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3 108 Ethics and dissemination
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5 109 PICUS is conducted according to the Declaration of Helsinki and Guideline for Good Clinical Practice.
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8 110 Five Medical Ethics Review Committees assessed PICUS. The results will be submitted for publication
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10 111 in an international peer-reviewed journal.
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16 113 Conclusion
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18 114 PICUS investigates the diagnostic yield of EUS in patients with a first episode of IAP and will determine
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20 115 whether routine EUS should be a part of the standard diagnostic work-up of a first episode of IAP.
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27 117 Trial registration
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29 118 Netherlands Trial Register: NL7066, June 9th 2018. Prospectively registered.
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38 121 Article summary: strengths and limitations
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40 122 • The PICUS study investigates the diagnostic yield of endoscopic ultrasonography in patients
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42 123 with a first episode of presumed idiopathic acute pancreatitis.
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45 124 • This is the first prospective cohort studies of patients with a single episode of presumed IAP
46
47 125 after complete standard diagnostic work-up (including exclusion based on blood serum ALT
48
49 126 and imaging after clinical recovery).
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52 127 • The results of the PICUS study will establish whether routine EUS should be incorporated in
53
54 128 the guidelines for standard diagnostic work-up after a first episode of presumed IAP.
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131 Keywords

132 Idiopathic acute pancreatitis; endoscopic ultrasonography, etiology

133

134

135 Background

136 Acute pancreatitis can be induced by numerous causes. Gallstone disease (approximately 50%) and
137 alcohol (approximately 20%) are the most frequent causes (1-6), although the prevalence of etiologies
138 of acute pancreatitis is dependent on, among other things, age and geographical factors (7-10). There
139 is, however, a considerable group of patients of approximately 25% in whom no etiology can be found
140 after routine diagnostic work-up (i.e. medical history, laboratory investigations and transabdominal
141 ultrasound). These patients are considered to have presumed idiopathic acute pancreatitis (IAP) (3).

142 When IAP is presumed, guidelines recommend repeat transabdominal ultrasound after
143 discharge (11, 12). This repeat ultrasonography has an additional diagnostic yield of 20% for the
144 detection of gallstones or sludge in these patients (13). Undetected microlithiasis and biliary sludge
145 are generally considered to be the major cause of presumed IAP (14, 15). Undetected and subsequently
146 untreated gallstone disease poses a risk for recurrent acute pancreatitis and other biliary events, e.g.
147 cholecystitis, biliary colic's and cholangitis.

148 Therefore, when previous diagnostics failed to uncover an etiology, endoscopic
149 ultrasonography (EUS) should be considered for the detection of biliary disease or other abnormalities
150 causing pancreatitis, such as neoplasms and chronic pancreatitis (11, 12, 16, 17). EUS is advised as the
151 first step in presumed IAP, followed by (secretin-stimulated) magnetic resonance
152 cholangiopancreaticography (MRCP) to identify rare morphologic abnormalities (11), as EUS is
153 considered to have a higher diagnostic yield than MRCP for clinically relevant causes (18).

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3 154 Although guidelines do recommend performing EUS after a first or second attack of presumed
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5 155 IAP, this recommendation is scored as a mere grade 2C, according to the GRADE classification (19)
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7 156 (indicating a weak recommendation based on evidence of low quality, with weak agreement among
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9 157 experts in this field) (11). Therefore, EUS is not routinely performed as the exact significance in this
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11 158 patient group is unclear (11, 16).

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15 159 The PICUS study was designed to determine whether routine EUS should be incorporated in
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17 160 the standard diagnostic work-up of a first episode of presumed IAP.

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24 25 26 163 **Methods and analysis**

27 28 29 164 **Study aim**

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31 165 The objective of this study is to determine the diagnostic yield of EUS for the detection of etiology in
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33 166 patients with a first episode of presumed IAP.

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36 167 Depending on the diagnostic yield of EUS observed in the PICUS study, incorporation of EUS
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38 168 in routine diagnostic work-up of patients with a first episode of presumed IAP will be considered. A
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40 169 minimal diagnostic yield of 10% for any etiology will be regarded as reasonable to justify implementing
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42 170 routine EUS in the standard diagnostic work-up of a first episode of presumed IAP.

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47 48 49 172 **Study design and setting**

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51 173 PICUS is a multicenter prospective cohort study. A total of 106 patients will be included from 28
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53 174 participating Dutch centers, including all 8 university centers and 20 large teaching hospitals. A listing
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55 175 of the participating centers is included in the Authors' information. An overview of the study design,
56
57 176 including screening procedures and follow-up, is provided in figure 1.

177

178 Study population

179 The subjects of this study have had a first episode of acute pancreatitis, as defined by the 2012 Revised
180 Atlanta criteria (20), with an unknown origin after standard diagnostic work-up, according to the 2013
181 IAP/APA evidence-based guidelines on management of acute pancreatitis (11). The diagnostic
182 modalities that constitute standard diagnostic work-up are listed in table 1. Potential etiologies and
183 their definitions are listed in table 2.

184

185 Eligibility criteria

186 The inclusion criteria are:

- 187 1. Patients of 18 years or older
- 188 2. First episode of presumed IAP after standard diagnostic work-up
- 189 3. Informed consent for participation

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191 The exclusion criteria are:

- 192 1. Known etiology
- 193 2. Chronic pancreatitis, as defined by the M-ANNHEIM criteria (21)
- 194 3. Recurrent pancreatitis
- 195 4. Altered anatomy which prohibits the endosonographer from visualizing the gall bladder, bile
196 ducts, pancreas or pancreatic duct via EUS (e.g. gastric bypass surgery)
- 197 5. Diagnostic EUS aimed to determine etiology before inclusion

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2
3 199 Endoscopic ultrasonography
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5 200 EUS will be performed in routine clinical practice by an endosonographer. Use of linear or radial EUS
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7 201 will be at the discretion of the endosonographer. All Dutch endosonographers are trained to perform
8
9 202 EUS according to the technique of Hawes and Fockens (22).
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13 203 The endosonographer will systematically report, using a standardized Case Report Form (CRF),
14
15 204 the experience of the endosonographer, visualization of anatomical structures (i.e. gall bladder,
16
17 205 common bile duct (CBD) and pancreatic duct), presence of local complications of acute pancreatitis,
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19 206 characteristics of biliary etiology (i.e. gallstones, microlithiasis and/or biliary sludge), characteristics of
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21 207 chronic pancreatitis, presence of (a) pancreatic or peri-ampullary benign or malignant tumor(s),
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23 208 characteristics of auto-immune pancreatitis, anatomic variations (e.g. pancreas divisum) or other
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25 209 anomalies (e.g. cholecystitis, vascular, renal, splenic or hepatic anomalies or ascites), and performance
26
27 210 of fine needle aspiration or fine needle biopsy. Additionally, the type of endoscope, use of sedation,
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29 211 procedure related complications and results of the fine needle aspiration or biopsy will be
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31 212 systematically recorded by the study coordinator in a separate CRF.
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39 214 Primary outcome measure
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41 215 The primary outcome measure is the number and ratio of patients with presumed IAP in whom EUS
42
43 216 detects a cause for the pancreatitis episode.
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46 217 A positive EUS is defined as an EUS during which a definitive cause for the acute pancreatitis
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48 218 episode has been found; or during which abnormalities are visualized constituting a definitive cause,
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50 219 after obtaining tissue and pathological examination. An overview of the exact findings scored as
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52 220 positive imaging is provided in table 3.
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56 221 If during EUS pancreatic abnormalities are found, yet not enough to make a certain diagnosis
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58 222 of chronic pancreatitis according to the M-ANNHEIM classification (21), this imaging is considered to
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3 223 be negative, even though it did show abnormalities. This approach is chosen because the aim of this
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5 224 study is to determine the rate of which EUS can find a cause for the presumed IAP episode. For the
6
7 225 same reason, report of an anatomical abnormality during EUS after a first episode of acute pancreatitis
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10 226 is not scored as positive imaging as pancreatic morphological changes are very common in IAP and not
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12 227 necessarily clinically relevant, as is elaborated on in the discussion (23).
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18 229 Secondary outcome measures

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20 230 The secondary outcome measures are recurrence rate of acute pancreatitis, severity of recurrent
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22 231 pancreatitis (20), readmission, performance of additional invasive procedures (e.g. cholecystectomy,
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24 232 endoscopic sphincterotomy), complications of EUS and of additional interventions, according to the
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27 233 Clavien-Dindo classification (24), length of hospital stay, quality of life, mortality and costs. Relevant
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29 234 definitions are reported in Additional File 2.
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35 236 Sample size calculation

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37 237 The sample size calculation was based on the primary outcome measure, diagnostic yield of EUS. Based
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40 238 on two previous studies reporting yield in patients with a first episode of presumed IAP (25, 26),
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42 239 adjusted for the PICUS study criteria for inclusion (i.e. requiring negative imaging after clinical
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44 240 recovery) and for positive imaging (i.e. excluding pancreas divisum as etiology), diagnostic yield was
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46 241 assumed to be 30%. Using a two-sided significance level (α) of 0.05, a power ($1 - \beta$) of 80%, 95 patients
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48 242 are needed to attain a 95% confidence interval (CI) with a range smaller than 10% above and below
49
50
51 243 the assumed yield of 30% (95% CI: 20.8, 39.2). Assuming a drop-out rate of 10%, a total of 106 patients
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53 244 will be included (27). The sample size was calculated using the software programs RStudio (28) and
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55 245 nQuery (29).
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3 247 Follow-up
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5 248 Data from patient records on primary and secondary outcome measures will be collected until 1 year
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7 249 after inclusion. Outpatient care and follow-up after the EUS is at the discretion of the treating
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10 250 physician, but an outpatient clinic visit after EUS to discuss the results of the EUS and potential
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12 251 subsequent appropriate treatment can be considered standard care.
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15 252 In case of biliary disease, the patient will be considered for endoscopic retrograde
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17 253 cholangiopancreatography (ERCP) with sphincterotomy when choledocho(-micro-)lithiasis or sludge
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19 254 in the CBD is present, and cholecystectomy, as is standard care for biliary pancreatitis. A (secretin-
20
21 255 stimulated) MRCP will be recommended, if not performed earlier, if a patient is readmitted for a
22
23 256 recurrent episode of acute pancreatitis after a negative EUS for etiology, in order to rule out structural
24
25 257 anomalies such as pancreas divisum. This is in accordance with current guidelines (11).
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29 258 Patients will be asked to fill out the Short Form-36 questionnaire in the validated Dutch
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31 259 translation on day 3 after inclusion, after 6 months and after 1 year.
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37 261 Statistical aspects
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39 262 All included subjects will be evaluated for primary and secondary endpoints until 1 year after inclusion.
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41 263 The primary analysis will be based on intention-to-treat principles. For exploratory reasons a per-
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43 264 protocol analysis will be performed too.
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47 265 The intention-to-treat population comprises all patients included in the study, regardless of
48
49 266 adherence to study protocol. The per-protocol population is the subset of included patients who were
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51 267 treated with the guidelines of the protocol. A tabular listing of all patients excluded from the intention-
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53 268 to-treat population will be provided together with the reasons for exclusion.
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3 269 All analyses will be performed in SPSS for Microsoft Windows. All data handling and analysis
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5 270 will be saved in a syntax-file. Results will be presented with all centers combined. A two-tailed p-value
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7 271 of < 0.05 is considered statistically significant.
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13 273 **Baseline variables**

15 274 The reported baseline characteristics consist of age, sex, body mass index (BMI), previous
16 275 cholecystectomy, nicotine and alcohol use, severity of pancreatitis, length of hospital stay, amylase,
17 276 lipase, C-reactive protein, alanine transaminase, calcium, albumin and triglycerides on admission,
18 277 imaging modalities before EUS and their findings. Baseline characteristics of EUS will include timing of
19 278 EUS, experience of endosonographer and type of sedation and type of endoscope used. Data will be
20 279 presented in percentages or as mean with standard deviation, or in case of a skewed distribution as
21 280 median with interquartile range (IQR).
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32 282 **Primary outcome measure: etiology detection rate**

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35 283 Overall detection rate of an etiology for the episode of acute pancreatitis will be presented as
36 284 percentage with a 95% CI. Predefined subgroup analyses will be made for patients with and without
37 285 obesity (cut-off at a BMI of 30), a previous cholecystectomy, alcohol use and local complications from
38 286 the IAP episode. A subgroup analysis will also be made for patients with a transabdominal ultrasound
39 287 as imaging after clinical recovery and with magnetic resonance imaging (MRI) or MRCP as imaging after
40 288 clinical recovery. Finally, a subgroup analysis will be made for EUS performed by endosonographers
41 289 with and without extensive experience (cut-off at 400 endosonographies performed), use of linear or
42 290 radial scope and type of sedation used. In subgroup analyses, the Chi-square test or the Fisher's exact
43 291 test will be used, as appropriate, to compare etiology detection rate between subgroups. In subgroup
44 292 analyses, comparability between groups regarding baseline variables will be checked. If the subgroups
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3 293 differ statistically significantly in one or more baseline variables, this will be corrected in a logistic
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5 294 regression analysis.
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11 296 ***Secondary outcome measures***
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14 297 Secondary outcome measures will be described as percentages with 95% CI, as mean with standard
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16 298 deviation or median with IQR, as appropriate.
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19 299 For recurrence rate, subgroup analyses will be made for patients with a positive and negative
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21 300 EUS, and in patients with a positive EUS, for patients who were and were not treated adequately. The
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23 301 same subgroup analyses as in the primary outcome measure, will also be applied on the recurrence
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25 302 rate. The Chi-square test or the Fisher's exact test will be used for comparison between subgroups, as
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27 303 appropriate.
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31 304 For quality of life, subgroup analyses will be made for baseline versus follow-up quality of life
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33 305 and for patients with a positive and negative EUS, and with and without pancreatitis recurrence during
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35 306 follow-up. The (un-)paired T-test, Wilcoxon signed rank test or the Mann-Whitney U test will be used
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37 307 for comparisons between subgroups, as appropriate.
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44 309 ***Cost analysis***
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46 310 The cost analysis will comprise direct medical costs, which are generated by healthcare utilization and
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48 311 include hospital admission periods and therapeutic and diagnostic procedures (30). Estimates of unit
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50 312 costs will be based on Dutch reference data from the cost guide of the Dutch Health Council (31). If
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52 313 this guide is an inappropriate determination of unit costs, the costs will be based on data provided by
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54 314 two hospital administrations (one university center and one general hospital) to account for the actual
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56 315 input of personnel, material and overhead over hospital resources used. Cost calculations will be used
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3 316 to determine cost of interventions (surgical, endoscopic or radiological) and diagnostic imaging. The
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5 317 cost analysis will be reported separately from the main study manuscript.
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11 319 Patient and public involvement

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14 320 The patient advocacy organization *Alvleesklievereniging Nederland* was involved in the design of the
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16 321 PICUS study. The experience of the patient advocacy organization with IAP and participation in
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18 322 scientific research has driven the research question and design of the study with regards to patient
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20 323 burden. The patient advocacy organization will also be involved in the dissemination and
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22 324 implementation of the study results.
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26 325 All patients eligible for participation will be asked to give written informed consent.
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34 328 Ethics and dissemination

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37 329 The PICUS study is conducted according to the principles of the Declaration of Helsinki (October 2013)
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39 330 and to the Guideline for Good Clinical Practice by the International Council for Harmonization
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41 331 (November 9 2016).
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43
44 332 The need for ethical approval was waived by the Medical Ethics Review Committee of the
45
46 333 Academic Medical Center on May 28, 2018 (W18_161 # 18.199), by the Medical Research Ethics
47
48 334 Committee of the University Medical Center Utrecht on July 04, 2018 (18-469), by the Research Ethics
49
50 335 Committee of Radboud university medical center on July 23, 2018 (2018-4520), by the Medical Ethics
51
52 336 Review Committee of the Erasmus Medical Center on July 30, 2018 (MEC-2018-1293) and by the
53
54 337 Medical Ethics Review Committee of the Maastricht University Medical Center on September 7, 2018
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56 338 (2018-0685). Before start of inclusion, local board approval will be obtained in all participating centers.
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3 339 The results of the PICUS study will be submitted for publication in an international peer-
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5 340 reviewed scientific journal, regardless of study outcomes.
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14 343 Discussion

16 344 Previous research has suggested that EUS might be beneficial in the detection of an etiology in
18 345 presumed IAP. However, data lacks on the efficacy of routine EUS in patients with a first episode of
20 346 presumed IAP, after repeat imaging after clinical recovery is negative for an etiology. The PICUS study
22 347 aims to determine whether routine EUS is warranted in a first episode of acute pancreatitis where no
24 348 cause could be disclosed after complete standard diagnostic work-up.

28 349 Currently, guidelines do not clearly define criteria for biliary origin (11). However, it is generally
30 350 agreed upon that cholelithiasis, microlithiasis or biliary sludge constitute biliary etiology. Several
32 351 previous studies have shown an association between elevated ALT levels and acute biliary pancreatitis
34 352 (32-35), with a positive predictive value of 85% for an ALT > 150 U/L within 48 hours after onset of
36 353 symptoms (11, 32, 33, 35). Therefore, an elevated blood serum ALT level at admission is considered to
38 354 entail a high probability of biliary etiology, and pancreatitis with an elevated ALT is treated as being of
40 355 biliary origin (32-34, 36). However, the majority of current literature on EUS did not exclude patients
42 356 based on ALT level at admission (15, 25, 26, 32, 37-46). As these patients have a higher a priori chance
44 357 of confirmation of biliary etiology on EUS, the etiology detection rate of EUS might be overestimated
46 358 in these studies. In PICUS, biliary etiology is defined as either the signs of cholelithiasis, microlithiasis
48 359 or biliary sludge on transabdominal ultrasonography, or transient elevation of the blood serum ALT
50 360 level of more than twice the upper limit of normal at admission. By only including patients with normal
52 361 or slightly elevated ALT levels at admission, the etiology detection rate as reported in PICUS will reflect
54 362 the detection rate in patients who are truly considered as having presumed IAP after standard
56 363 diagnostic work-up.

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3 364 Current guidelines advise a repeat transabdominal ultrasound after clinical recovery in the
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5 365 work-up of presumed IAP because the index transabdominal ultrasound is less sensitive during the
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7 366 acute phase of pancreatitis. The subpar visualization of gall bladder, bile ducts and pancreas is often
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10 367 due to excessive amounts of air in the intestines caused by pancreatitis-induced ileus and/or
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12 368 suboptimal cooperation of painful patients (47). After the first episode of acute pancreatitis, repeating
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14 369 a transabdominal ultrasound may be able to detect biliary stones where it could not during index
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16 370 admission (48). However, of the current literature on EUS in IAP, only a minority of studies included
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18 371 repeat imaging in the diagnostic work-up before EUS (15, 40, 41, 43). Previous research has shown that
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20 372 a repeat transabdominal ultrasound has a diagnostic yield of 20% in patients with a first episode of IAP
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22 373 (13). Omitting repeat imaging from diagnostic work-up before EUS may lead to an overestimation of
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24 374 the diagnostic yield of EUS. In PICUS, all patients are required to undergo imaging after clinical
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26 375 recovery, i.e. transabdominal ultrasound or MRI/MRCP. Computed tomography (CT) is not considered
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28 376 sufficient imaging as biliary disease, the most common underlying etiology in presumed IAP, cannot
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30 377 always be adequately detected using CT.
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35 378 It is well documented that the overall diagnostic yield of EUS in patients with recurrent
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37 379 pancreatitis is superior to the diagnostic yield of both secretin-stimulated MRCP (s-MRCP) and non-
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39 380 secretin-stimulated MRCP (18, 44, 46, 49). In the subgroup of patients with a pancreas divisum,
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41 381 however, s-MRCP is considered to be superior in diagnostic yield to both EUS and MRCP (18). The role
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43 382 of pancreas divisum in the etiology of pancreatitis is unclear. Epidemiological studies have shown that
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45 383 the prevalence of pancreas divisum in the general population is equal to the prevalence in patients
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47 384 with presumed IAP (23). In patients with a pancreas divisum and acute pancreatitis, potentially other
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49 385 disease modifying factors add to the occurrence of pancreatitis, such as increased sensitivity to toxins
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51 386 or genetic susceptibility. Because of this ambiguity, pancreas divisum in patients with a first episode
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53 387 of acute pancreatitis is mostly left untreated in clinical practice. However, if patients with a pancreas
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55 388 divisum present with multiple episodes of presumed IAP, the divisum is often considered to be related
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57 389 to the pancreatitis and is subsequently treated, often with ERCP with endoscopic sphincterotomy,
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3 390 although evidence supporting this practice is limited (23). Because of both the diagnostic superiority
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5 391 of EUS in recurrent pancreatitis as well as the lack of clinical consequences of (s-)MRCP in patients with
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7 392 a first episode of pancreatitis, EUS is preferred to (s-)MRCP as the first choice for additional diagnostic
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10 393 testing for etiology in patients with presumed IAP (18, 44, 46, 49). Subsequently, current guidelines
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12 394 advise performing MCRP in case of recurrent IAP after EUS fails to determine an etiology (11).
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14 395 Therefore, in PICUS, we have chosen not to systematically include (s-)MRCP in the diagnostic work-up
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16 396 before EUS of first episode IAP.

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19 397 Current guidelines advise consideration of EUS after a first or second attack of IAP (11).
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22 398 However, there is a paucity of evidence on the efficacy of EUS in first episode IAP. Three previous
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24 399 studies prospectively reported on EUS in patients with first episode IAP (25, 26, 38). However, in these
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26 400 studies, patients were not excluded based on liver enzymes abnormalities suggestive of biliary disease
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28 401 and no repeat imaging after clinical recovery was performed. PICUS will be the first prospective cohort
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30 402 study in which EUS will be performed in patients with a first episode of IAP after complete standard
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32 403 diagnostic work-up before EUS according to current guidelines (11).
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36 404 A diagnostic yield of 10% for any etiology will be considered reasonable to justify incorporating
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38 405 routine EUS after a first episode of presumed IAP. This cut-off value was determined during a
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40 406 multidisciplinary meeting of the Dutch Pancreatitis Study Group, which included the principal
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42 407 investigators of several trials being executed by the Dutch Pancreatitis Study Group. Considering the
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44 408 expectation that the majority of uncovered etiologies by EUS will be treatable (e.g. biliary disease) and
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46 409 adequate treatment could prevent pancreatitis recurrence, while in a minority of uncovered etiologies
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48 410 diagnosis before progression of disease might be crucial for prognosis (e.g. malignancy), a positive
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50 411 result in 10% of patients was deemed sufficient to warrant routine EUS after a first episode of
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52 412 presumed IAP.
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57 413 In conclusion, the PICUS study is the first prospective cohort study of patients with a single
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59 414 episode of presumed IAP after complete standard diagnostic work-up (including exclusion based on
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3 415 blood serum ALT and imaging after clinical recovery). The results of the PICUS study will establish
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5 416 whether routine EUS should be incorporated in the guidelines for standard diagnostic work-up after a
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7 417 first episode of presumed IAP.
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3 614 Author Statement
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6 615 Authors' contributions
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8 616 DSU drafted the manuscript. HCT, RCV, SAB, MGB and JEvH co-authored the writing of the manuscript.
9

10 617 DSU, RCV, SAB, MABo, MJB, PF, EJMvG, JWP, HCvS, FPV, MGB and JEvH were involved in the design of
11

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13

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16 620 RLJvW and BJW critically assessed the study design, during several meetings, and edited the
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28

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31 626 design, implementation and conduct of the study, as well as on collection, analysis and interpretation
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33 627 of data, construction of the manuscript and decision to publish.
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40 629 Competing interests statement
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42 630 The authors declare that they have no competing interests.
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48 632 Data Availability Statement
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50 633 The datasets used and/or analyzed during the current study are available from the corresponding
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52 634 author on reasonable request.
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637 Figure legend

638 Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP = magnetic
 639 resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic ultrasonography.

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641

642 Table 1

Standard diagnostic work-up	
<i>Detailed personal and family history, including questions on:</i>	Alcohol use
	Recent ERCP
	Recent start or changes in use of drugs associated with acute pancreatitis
	Recent major abdominal trauma
	Recent abdominal surgery
	Familial and hereditary pancreatitis
	Cystic fibrosis-related pancreatitis
<i>Laboratory tests, including:</i>	Blood serum triglycerides level
	Blood serum calcium level, corrected for the blood serum albumin level
	Blood serum ALT level on admission
<i>Imaging:</i>	Transabdominal ultrasound, MRI or MRCP after clinical recovery

643 **Table 1: Standard diagnostic work-up** Standard diagnostic work-up according to the 2013 IAP/APA evidence-based guideline
 644 on management of acute pancreatitis. A listing of the drugs considered to be associated with acute pancreatitis are listed in
 645 additional file 1. ERCP = endoscopic retrograde cholangiopancreatography; ALT = alanine aminotransferase; MRI = magnetic
 646 resonance imaging; MRCP = magnetic resonance cholangiopancreatography.

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648

649 Table 2

Etiology	Definition
Alcohol	> 4 units of alcohol in the 24 hours prior to start of abdominal complaints (50-52)
Biliary disease	<ol style="list-style-type: none"> 1. A transient elevated ALT level of >2 times the upper limit of normal at diagnosis of acute pancreatitis (34), OR 2. Gallstones, microlithiasis and/or biliary sludge, OR 3. A dilated CBD of >8 mm in patients <76 years or >10 mm in patients >75 years at diagnosis of acute pancreatitis (53)
Cystic fibrosis	history of cystic fibrosis in the absence of another origin (54)
Familial	two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis (55-57)
Hereditary	mutation in the PRSS1, SPINK1, CFTR, CTSC, CLDN2 or CPA1 gene, or direct family member (parents, children, siblings) with one or more of the above mentioned mutations and at least one direct family member who has (had) acute or chronic pancreatitis (57, 58)
Hypercalcemia	blood serum calcium level ≥ 12 mg/dl (3 mmol/l), corrected for serum albumin level, as first measured during admission (59)
Hypertriglyceridemia	blood serum triglyceride level of ≥ 1000 mg/dl (11.2 mmol/l) under fasting conditions, as first measured during admission (60)
Medication	use of drug(s) listed in additional file 1, which has or have been started or increased in dosage within a reasonable temporal sequence, in principle 1

	month before onset of pancreatitis, and has or have a positive dechallenge (a drug reaction that is confirmed by stopping the drug) (61, 62)
Neoplasm	Known hepatopancreatobiliary malignancy or known malignancy with metastases causing obstruction of the pancreatic duct (63)
ERCP	ERCP within 24 hours before diagnosis of pancreatitis (64)
Surgical	abdominal surgery within 24 hours prior to diagnosis of pancreatitis (65)
Trauma	typical blunt trauma to the upper abdomen and pancreatic trauma visible on imaging (66)

650 **Table 2: potential etiologies and their definitions** Potential etiologies and their definitions. Side branch or mixed type
 651 *intraductal papillary mucinous neoplasms without dilatation of the pancreatic duct and pancreas divisum will not be*
 652 *considered to be a causative factor for the pancreatitis episode. If imaging is not able to discriminate between gall bladder*
 653 *polyps or concrements, lesions smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm,*
 654 *irrespective of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and these patients*
 655 *will be excluded from PICUS. ALT = alanine transaminase. CBD = common bile duct. ERCP = endoscopic retrograde*
 656 *cholangiopancreatography.*

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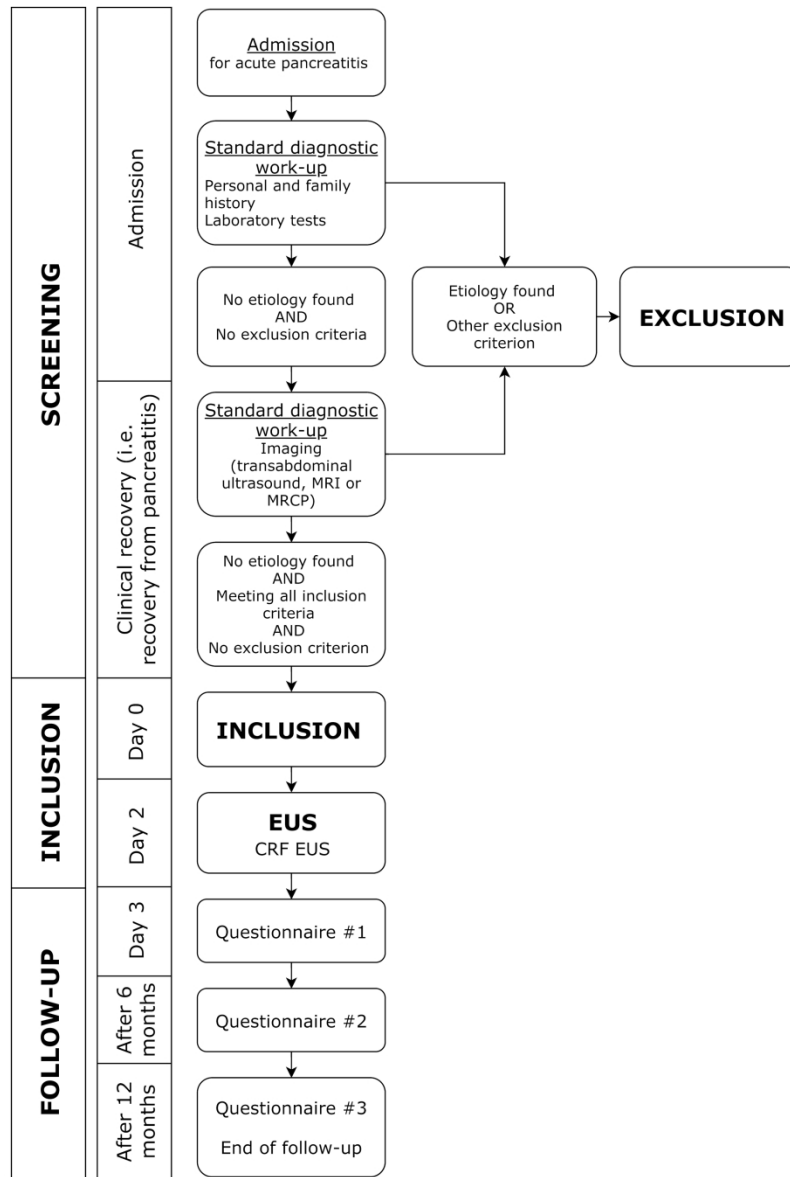
659 **Table 3**

<i>Biliary pancreatitis</i>	Presence of biliary stones, microlithiasis, or sludge
	Widened CBD, >8 mm in patients <76 years, or >10 mm in patients >75 years, in the absence of other CBD dilating factors (e.g. opioid use, distal stenosis, obstruction of external compression of CBD or papilla (67))
<i>Chronic pancreatitis</i>	Pancreatic calcifications
	> 4 of the following abnormal features of the pancreas:

	<ol style="list-style-type: none"> 1. Enlarged gland size 2. Cysts 3. Echo-poor lesions (focal areas of reduced echogenicity) 4. Echo-rich lesions (> 3 mm in diameter) 5. Accentuation of lobular pattern 6. Increased duct wall echogenicity 7. Irregularity of the main pancreatic duct 8. Dilation of the main pancreatic duct > 3.5 mm (68) 9. Visible side branches 10. Calcifications of the pancreatic duct
<i>Neoplasms</i>	Definitive diagnosis of pathological tissue after histological or cytological evaluation of specimen of an anomaly observed during EUS, e.g. hyperplastic or malignant tissue, or auto-immune inflammatory disease
	Main duct IPMN or mixed type IPMN causing dilatation of the pancreatic duct

660 **Table 3: positive imaging** Definition of positive imaging. For each diagnosis, presence of one of the separately mentioned
661 abnormalities is required to be considered as positive imaging. Specimen is not required to be obtained during EUS. Anatomical
662 anomalies (e.g. divisum) are not considered a certain etiology in first episode IAP and therefore not considered as positive
663 imaging. CBD = common bile duct. EUS = endoscopic ultrasonography. IPMN = intraductal papillary mucinous neoplasm.

664



Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP = magnetic resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic ultrasonography.

105x154mm (600 x 600 DPI)

Additional file 1: Table S1 Drugs associated with acute pancreatitis

Drugs associated with acute pancreatitis				
Acetaminophen	Cisplatin	Hydrochlorothiazide	Methyldopa	Pentavalent antimony compounds
Asparaginase	Cytarabine	Interferon alpha	Metronidazole	
Azathioprine	Didanosine	Itraconazole	Octreotide	Phenformin
Bortezomib	Enalapril	Lamivudine	Olanzapine	Simvastatin
Capecitabine	Erythromycin	Mercaptopurine	Opiates	Steroids
Carbamazepine	Estrogens	Mesalazine	Oxyphenbutazone	Sulfasalazine
Cimetidine	Furosemide	Olsalazine	Pentamidine	co-trimoxazole

Drugs with a definite association with acute pancreatitis (1, 2)

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1 Additional file 2: Relevant definitions

2 Acute pancreatitis: an acute inflammation of the pancreatic parenchyma, diagnosed when at least two
3 of the three following characteristics are present (1):

- 4 1. Clinical features of acute pancreatitis, such as upper abdominal pain
- 5 2. Elevated serum amylase or lipase levels of at least three times the upper limit of normal (ULN)
- 6 3. Signs of acute pancreatitis on imaging

7 Note: no value of the required serum amylase or lipase level is provided as every participating center
8 has a local laboratory, which is why each center may use different normal range values.

9
10 Idiopathic acute pancreatitis is considered to be present if no etiology is found in standard work-up,
11 which comprises at least the following tests:

- 12 1. A detailed personal and family history, including questions on:
 - 13 a. Alcohol use
 - 14 b. Recent endoscopic retrograde cholangiopancreatography (ERCP)
 - 15 c. Recent start of or changes in use of drugs associated with acute pancreatitis
 - 16 d. Recent major abdominal trauma
 - 17 e. Recent abdominal surgery
 - 18 f. Familial pancreatitis
 - 19 g. Hereditary pancreatitis
 - 20 h. Cystic fibrosis related pancreatitis

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2
3 21 2. Laboratory tests, including:
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6 22 a. Blood serum triglycerides level on admission
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9 23 b. Blood serum calcium level, corrected for the serum albumin level, on admission
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12 24 c. Blood serum alanine transaminase (ALT) level on admission
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15 25 3. Imaging via transabdominal ultrasound, magnetic resonance imaging (MRI) or magnetic
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17 26 resonance cholangiopancreatography (MRCP) after clinical recovery
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20 27 Note: side branch or mixed type intraductal papillary mucinous neoplasms (IPMN) without dilatation
21
22 28 of the pancreatic duct will not be considered to be a causative factor for the pancreatitis episode.
23

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25 29 Note: if the imaging is not able to discriminate between gall bladder polyps or concrements, lesions
26
27 30 smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm, irrespective
28
29 31 of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and
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31 32 will be excluded from PICUS.
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35 34 Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when biliary
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37 35 etiology is not demonstrated by standard work-up and the patient has indicated (either by direct or
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39 36 indirect personal history or by findings during physical examination) to have drunk at least five units of
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41 37 alcohol in the 24 hours prior to start of abdominal complaints (or in asymptomatic acute pancreatitis:
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43 38 prior to diagnosis) (2-4)
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52 40 Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one
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54 41 of the following features is present:
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57 42 1. A transient elevated ALT level of more than two times the ULN at diagnosis of acute
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59 43 pancreatitis (5)
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3 44 2. Signs of presence of gallstones, microlithiasis or sludge on imaging, defined as follows:
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6 45 a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus
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8 46 cysticus, intrahepatic bile ducts or in the common bile duct (CBD), and/or
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11 47 b. A CBD of more than eight mm in patients 75 years old or younger or more than ten
12
13 48 mm in patients older than 75 years at diagnosis of acute pancreatitis (6)
14
15

16 49 Note: no value of the required serum ALT level is provided as the normal range values depend on the
17
18 50 sex of the patient and as every participating center has a local laboratory, which is why each center
19
20 51 may use different normal range values.
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26 53 Chronic pancreatitis: a chronic inflammation of the pancreatic parenchyma, defined as typical clinical
27
28 54 history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary
29
30 55 painless pancreatitis) and one or more of the following (7):
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34 56 1. Pancreatic calcifications
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37 57 2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features
38
39 58 on transabdominal ultrasound, computed tomography (CT) or MRI/MRCP, according to the
40
41 59 Cambridge classification (8):
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43
44 60 a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of
45
46 61 the duct wall (mandatory)
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48
49 62 b. Pancreatic enlargement
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52 63 c. Cavities
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55 64 d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
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58 65 e. Focal acute pancreatitis
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- 3 66 f. Parenchymal heterogeneity
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- 6 67 g. Irregularities of pancreatic head or body contour
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- 9 68 3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features
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- 11 69 on endoscopic ultrasonography (EUS):
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- 14 70 a. Enlarged gland size
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- 16
- 17 71 b. Cysts
- 18
- 19
- 20 72 c. Echo-poor lesions (focal areas of reduced echogenicity)
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- 23 73 d. Echo-rich lesions (more than three mm in diameter)
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- 25
- 26 74 e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by
- 27
- 28 75 hyperechoic strands)
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- 30
- 31 76 f. Increased duct wall echogenicity
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- 33
- 34 77 g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
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- 37 78 h. Dilation of the main pancreatic duct
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- 40 79 i. Visible side branches (e.g., with dilation)
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- 43 80 j. Calcification (of the pancreatic duct)
- 44
- 45 81 4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly
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- 47 82 reduced by enzyme supplementation
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- 50 83 5. Typical histology of an adequate histological specimen
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53 84 Note: during initial diagnostic work-up during admission 'marked and persistent exocrine insufficiency'

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55 85 cannot be evaluated properly. Therefore this part of the definition of chronic pancreatitis will not be

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58 86 applicable during standard work-up. However, if the patient does show marked and persistent

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60 87 exocrine insufficiency during follow-up (either during the outpatient clinic visit after repeat

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3 88 transabdominal ultrasound or after the EUS), this will be considered to be diagnostic for chronic
4
5 89 pancreatitis. The same is applicable for histology of an adequate histological specimen: this is not part
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7 90 of standard work-up, however, if a typical histological specimen is obtained during follow-up, this will
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9 91 be considered to be diagnostic for chronic pancreatitis.
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15 93 Cystic fibrosis: an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in
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17 94 defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride
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19 95 greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both (9).
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25 97 Cystic fibrosis related pancreatitis: pancreatitis caused by defective ductular and acinar pancreatic
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27 98 secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis
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29 99 in the absence of another origin (9).
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35 101 Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that
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37 102 is greater than would be expected by chance alone, given the size of the family and the standardized
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39 103 incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who
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41 104 have two or more direct blood-related family members (parents, children or siblings) who have had an
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43 105 episode of acute pancreatitis (10-12).
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50 107 Fever: a body temperature of 38.5°C or higher.
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56 109 Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the
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58 110 pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in
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3 111 an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the
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5 112 PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTRC gene, the CLDN2 gene or the CPA1 gene, or if
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7 113 the patient has a direct family member (parents, children, siblings) with one or more of the above
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10 114 mentioned mutations and has at least one direct family member who has had an episode of acute
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12 115 pancreatitis or has chronic pancreatitis (12, 13).

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18 117 Hypercalcemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs
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20 118 of a biliary pancreatitis are found in standard work-up and the patient has a blood serum calcium level
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22 119 of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during
23
24 120 admission (14).

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29
30 122 Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if
31
32 123 a biliary etiology is not demonstrated by standard work-up and the patient has a blood serum
33
34 124 triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured
35
36 125 during admission (15).

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43 127 Hypothermia: a body temperature of 35.9°C or lower.

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49 129 Infected (extra)pancreatic necrosis: presence of microorganisms in (extra-)pancreatic necrosis,
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51 130 confirmed by a positive culture obtained by means of fine needle aspiration or from the first drainage
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53 131 procedure or necrosectomy, the presence of gas in the (extra-)pancreatic collection on CT, or the
54
55 132 presence of clinical signs of persistent sepsis or progressive clinical deterioration despite maximal
56
57 133 support on the intensive care unit (ICU) without other causes for infection (ruled out should be:

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3 134 pneumonia, urinary tract infection, wound infection, endocarditis, abdominal sepsis or any other
4
5 135 infection which could be suspected based on the individual patient's clinical presentation) (16).
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10 137 Medication associated pancreatitis: acute pancreatitis is considered to be caused by drugs when a
11
12 138 biliary cause is not demonstrated by standard work-up, the patient uses one or multiple drug(s) listed
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14 139 in table S1 in additional file 1, the drug has been started or increased in dosage within a reasonable
15
16 140 temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive
17
18 141 dechallenge (a drug reaction that is confirmed by stopping the drug) (17, 18).
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24 143 Microlithiasis: stones or concrements, smaller than four mm, in the gall bladder or the bile ducts (19).
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30 145 Murphy's sign: the phenomenon where compression of the right upper quadrant causes the patient
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32 146 to catch their breath due to pain when taking a deep breath (20).
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37
38 148 Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two
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40 149 separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one
41
42 150 main duct (of Wirsung) (21).
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48 152 Positive imaging: positive imaging is defined as imaging during which a definitive cause for the acute
49
50 153 pancreatitis episode can be found; or during which abnormalities are visualized constituting a
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52 154 definitive cause, after obtaining tissue and pathological examination. So, if during EUS ductal
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54 155 abnormalities are found, yet not enough to make a certain diagnosis of chronic pancreatitis according
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56 156 to the M-ANNHEIM classification (7), this imaging is considered to be negative, even though it did show
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58 157 abnormalities. This approach is chosen because the aim of this study is to determine the rate of which
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2
3 158 EUS can find a causative factor for a previous acute pancreatitis episode. For the same reason, finding
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5 159 of an anatomical abnormality after a first episode of acute pancreatitis is not scored as positive
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7 160 imaging. An overview of the exact findings scored as positive imaging is provided in table 3 of the main
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10 161 manuscript.

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16 163 Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic
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18 164 injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24
19
20 165 hours of an ERCP without indications of another origin (22).

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26 167 Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas,
27
28 168 diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of
29
30 169 indications for another origin (23).

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36 171 Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen,
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38 172 diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic
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40 173 trauma is visible on imaging (24).

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43 174
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46 175 Recurrence rate: the risk of a recurrent episode of acute pancreatitis.

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52 177 Sludge: solid material which results from the slow settling of particles dispersed in bile (19).

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3 180 Standard work-up:
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6 181 1. A detailed personal and family history, including questions on:
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8
9 182 a. Alcohol use
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12 183 b. Recent ERCP
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15 184 c. Recent start of or changes in use of drugs associated with acute pancreatitis
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18 185 d. Recent major abdominal trauma
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21 186 e. Recent abdominal surgery
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24 187 f. Familial pancreatitis
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27 188 g. Hereditary pancreatitis
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30 189 h. Cystic fibrosis related pancreatitis
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32 190 2. Laboratory tests, including:
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35 191 a. Blood serum triglycerides level, first measured during admission
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38 192 b. Blood serum calcium level, corrected for the serum albumin level, first measured
39 during admission
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43 194 c. Blood serum ALT level on admission
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46 195 3. Imaging via transabdominal ultrasound, MRI or MRCP after clinical recovery
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52 197 Biliary events: acute cholecystitis; biliary colic's requiring readmission; biliary pancreatitis; cholangitis;
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54 198 or obstructive choledocholithiasis needing ERCP.
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3 200 Acute cholecystitis: an acute inflammation of the gall bladder, diagnosed when one item in A, B and C

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5 201 is present:

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8 202 A) Local signs of inflammation

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11 203 1. Murphy's' sign, or

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14 204 2. Right upper abdominal quadrant mass, pain or tenderness

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17 205 B) Systemic signs of inflammation

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20 206 1. Fever or hypothermia, or

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23 207 2. Elevated C-reactive protein (CRP), or

24
25
26 208 3. Elevated white blood cell count

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29 209 C) Imaging findings characteristic of acute cholecystitis (25, 26)

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31 210 Note: acute cholecystitis and cholangitis are defined according to the Tokyo classification which
32 211 defines fever as a body temperature of 38°C or higher; however, fever will be defined in this study as
33 212 hyperthermia of 38.5°C or higher and hypothermia will be added as a systemic sign of inflammation,
34 213 as this more accurately reflects clinical practice in the Netherlands.

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44 215 Biliary colic: upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30
45 216 minutes, often associated with restlessness (27).

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51 218 Cholangitis: an inflammation of the bile duct(s), diagnosed when one item in each of the following
52 219 categories is present:

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56 220 1. Systemic inflammation

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58
59 221 a. Fever, hypothermia and/or shaking chills

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3 222 b. Laboratory data: evidence of inflammatory response (abnormal white blood cell
4
5 223 counts (defined as smaller than 4,000/ μ l or larger than 10,000/ μ l), increase of serum
6
7 224 CRP levels (defined as 1 mg/dl or higher), and other changes indicating inflammation)
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9

10 225 2. Cholestasis
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13 226 a. Jaundice (defined as a total bilirubin of 2 mg/dl or higher)
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16 227 b. Laboratory data: abnormal liver function tests (increased serum alkaline phosphatase,
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18 228 gamma-glutamyltransferase (gamma-GT), aspartate transaminase (AST) and ALT
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20 229 levels (defined as more than 1.5 times the ULN))
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23 230 3. Imaging
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26 231 a. Biliary dilatation
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29 232 b. Evidence of the etiology on imaging (stricture, stone, stent etc.) (25)
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31

32 233 Note: acute cholecystitis and cholangitis are defined according to the Tokyo classification which
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34 234 defines fever as a body temperature of 38°C or higher; however, fever will be defined in this study as
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36 235 hyperthermia of 38.5°C or higher and hypothermia will be added as a systemic sign of inflammation,
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38 236 as this more accurately reflects clinical practice in the Netherlands.
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45 238 Obstructive choledocholithiasis: presence of gallstones, microlithiasis or biliary sludge in the CBD on
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47 239 imaging, requiring an ERCP, according to the treating physician.
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255 Hansen, Hjalmar C. van Santvoort, Robin Timmer, Marie-Paule G. F. Anten, Clemens J. M. Bolwerk, Foke van
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257 Hulst, Jeroen M. Jansen, Frank J. G. M. Kubben, Sjoerd D. Kuiken, Lars E. Perk, Rogier J. J. de Ridder, Marno C.
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15 274 [I&HD=180221-1109&HDR=G1&STB=T](http://statline.cbs.nl/Statweb/publication/?VW=T&DM=SLNL&PA=37312&D1=a&D2=0,5,10,(I-2)-I&HD=180221-1109&HDR=G1&STB=T).
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 7, 9-14, 22, 23
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 23
	5b	Name and contact information for the trial sponsor	24
	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	23

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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) 24-26

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 8, 9

6b Explanation for choice of comparators Not applicable

Objectives 7 Specific objectives or hypotheses 9

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) 9

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 9

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) 10, 11

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 11

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) Not applicable

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4		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
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7		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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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	12-14
10				
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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)	Figure
15				
16				
17	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	14
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22	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
23				
24	Methods: Assignment of interventions (for controlled trials)			
25	Allocation:			
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28	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	Not applicable
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34	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	Not applicable
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Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial	Not applicable

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	11, 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	14, 15
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	11, 14, 15
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	15-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-17
	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)	15

Methods: Monitoring

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4	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	22
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9		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	Not applicable
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12	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, 15
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15	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	22
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19	Ethics and dissemination			
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21	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
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23	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)	22
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27	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
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31		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
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34	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	11, 14-17
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37	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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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	22
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	Not applicable
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	23
	31b	Authorship eligibility guidelines and any intended use of professional writers	23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon request
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	Not applicable

*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

The role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035504.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2020
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Secondary Subject Heading:	Evidence based practice, Research methods
Keywords:	Endoscopy < GASTROENTEROLOGY, Hepatobiliary disease < GASTROENTEROLOGY, Pancreatic disease < GASTROENTEROLOGY

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4 1 The role of endoscopic ultrasonography in the diagnostic work-up of
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7 2 idiopathic acute pancreatitis (PICUS): study protocol for a nationwide
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11 3 prospective cohort study
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53 66 List of abbreviations
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56 67 ALT = alanine aminotransferase
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59 68 BMI = body mass index
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3 69 CI = confidence interval
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6 70 CRF = case report form
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9 71 CT = computed tomography
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12 72 ERCP = endoscopic retrograde cholangiopancreatography
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15 73 EUS = endoscopic ultrasonography
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18 74 GRADE = Grading of Recommendations Assessment, Development and Evaluation
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21 75 IAP = idiopathic acute pancreatitis
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24 76 IAP/APA = International Association of Pancreatology/American Pancreatic Association
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27 77 IPMN = intraductal papillary mucinous neoplasm
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30 78 IQR = interquartile range
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33 79 MRCP = magnetic resonance cholangiopancreatography
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36 80 MRI = magnetic resonance imaging
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45 83 **Word count**

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52 86
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1
2
3 88 Abstract
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5
6 89 Introduction
7

8 90 Idiopathic acute pancreatitis (IAP) remains a dilemma for physicians as it is uncertain whether patients
9
10 91 with IAP may actually have an occult etiology. It is unclear to what extent additional diagnostic
11
12 92 modalities such as endoscopic ultrasonography (EUS) are warranted after a first episode of IAP in order
13
14 93 to uncover this etiology. Failure to timely determine treatable etiologies delays appropriate treatment
15
16 94 and might subsequently cause recurrence of acute pancreatitis. Therefore, the aim of the “Pancreatitis
17
18 95 of Idiopathic origin: Clinical added value of endoscopic UltraSonography” (PICUS) study is to determine
19
20 96 the value of routine EUS in determining the etiology of pancreatitis in patients with a first episode of
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22 97 IAP.
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30 99 Methods and analysis

31
32 100 PICUS is designed as a multicenter prospective cohort study of 106 patients with a first episode of IAP
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34 101 after complete standard diagnostic work-up, in whom a diagnostic EUS will be performed. Standard
35
36 102 diagnostic work-up will include a complete personal and family history, laboratory tests including
37
38 103 serum alanine aminotransferase, calcium and triglyceride levels, and imaging by transabdominal
39
40 104 ultrasound, magnetic resonance imaging or magnetic resonance cholangiopancreatography after
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42 105 clinical recovery from the acute pancreatitis episode. The primary outcome measure is detection of
43
44 106 etiology by EUS. Secondary outcome measures include pancreatitis recurrence rate, severity of
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46 107 recurrent pancreatitis, readmission, additional interventions, complications, length of hospital stay,
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48 108 quality of life, mortality and costs, during a follow-up period of 12 months.
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3 110 Ethics and dissemination
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5 111 PICUS is conducted according to the Declaration of Helsinki and Guideline for Good Clinical Practice.
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7
8 112 Five Medical Ethics Review Committees assessed PICUS. The results will be submitted for publication
9

10 113 in an international peer-reviewed journal.
11
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16 115 Trial registration
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18 116 Netherlands Trial Register: NL7066, June 9th 2018. Prospectively registered.
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27 119 Article summary: strengths and limitations
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29
30 120 • This is the first prospective cohort study of only patients with a single episode of presumed
31 121 IAP.
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33

34 122 • This is the first prospective cohort study which only includes patients after complete
35 123 standard diagnostic work-up (including exclusion based on blood serum ALT and imaging
36 124 after clinical recovery).
37
38

39 125 • The multicenter nature of this study reduces the risk of patient selection bias.
40
41

42 126 • By following patients for a year after EUS, this study could establish the association between
43 127 EUS, detection of etiology and subsequent treatment of etiology, and pancreatitis
44 128 recurrence.
45
46

47 129 • As the timing of the EUS is set to be after clinical recovery from pancreatitis in this trial, no
48 130 conclusions on the diagnostic yield of EUS in a different time frame can be drawn from this
49 131 study.
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3 133 **Keywords**
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6 134 Idiopathic acute pancreatitis; endoscopic ultrasonography, etiology
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15 137 **Background**
16

17 138 Acute pancreatitis can be induced by numerous causes. Gallstone disease (approximately 50%) and
18
19 139 alcohol (approximately 20%) are the most frequent causes (1-6), although the prevalence of etiologies
20
21
22 140 of acute pancreatitis is dependent on, among other things, age and geographical factors (7-10). There
23
24 141 is, however, a considerable group of patients of approximately 25% in whom no etiology can be found
25
26 142 after routine diagnostic work-up (i.e. medical history, laboratory investigations and transabdominal
27
28 143 ultrasound). These patients are considered to have presumed idiopathic acute pancreatitis (IAP) (3).
29
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32 144 When IAP is presumed, guidelines recommend repeat transabdominal ultrasound after
33
34 145 discharge (11, 12). This repeat ultrasonography has an additional diagnostic yield of 20% for the
35
36 146 detection of gallstones or sludge in these patients (13). Undetected microlithiasis and biliary sludge
37
38 147 are generally considered to be the major cause of presumed IAP (14, 15). Undetected and subsequently
39
40 148 untreated gallstone disease poses a risk for recurrent acute pancreatitis and other biliary events, e.g.
41
42 149 cholecystitis, biliary colic's and cholangitis.
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46 150 Therefore, when previous diagnostics failed to uncover an etiology, endoscopic
47
48 151 ultrasonography (EUS) should be considered for the detection of biliary disease or other abnormalities
49
50 152 causing pancreatitis, such as neoplasms and chronic pancreatitis (11, 12, 16, 17). EUS is advised as the
51
52 153 first step in presumed IAP, followed by (secretin-enhanced) magnetic resonance
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54 154 cholangiopancreaticography (MRCP) to identify rare morphologic abnormalities (11), as EUS is
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56 155 considered to have a higher diagnostic yield than MRCP for clinically relevant causes (18).
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3 156 Although guidelines do recommend performing EUS after a first or second attack of presumed
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5 157 IAP, this recommendation is scored as a mere grade 2C, according to the Grading of Recommendations
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7 158 Assessment, Development and Evaluation (GRADE) classification (19) (indicating a weak
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10 159 recommendation based on evidence of low quality, with weak agreement among experts in this field)
11
12 160 (11). Therefore, EUS is not routinely performed as the exact significance in this patient group is unclear
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14 161 (11, 16).

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17 162 The PICUS study was designed to determine whether routine EUS should be incorporated in
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19 163 the standard diagnostic work-up of a first episode of presumed IAP.
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28 166 Methods and analysis

29 167 Study aim

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31 168 The objective of this study is to determine the diagnostic yield of EUS for the detection of etiology in
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33 169 patients with a first episode of presumed IAP.
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39 170 Depending on the diagnostic yield of EUS observed in the PICUS study, incorporation of EUS
40
41 171 in routine diagnostic work-up of patients with a first episode of presumed IAP will be considered. A
42
43 172 minimal diagnostic yield of 10% for any etiology will be regarded as reasonable to justify implementing
44
45 173 routine EUS in the standard diagnostic work-up of a first episode of presumed IAP.
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50 51 175 Study design and setting

52
53 176 PICUS is a multicenter prospective cohort study. A total of 106 patients will be included from 28
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55 177 participating Dutch centers, including all 8 university centers and 20 large teaching hospitals. A listing
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3 178 of the participating centers is included in the Authors' information. An overview of the study design,
4
5 179 including screening procedures and follow-up, is provided in figure 1.
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11 181 Study population

13 182 The subjects of this study have had a first episode of acute pancreatitis, as defined by the 2012 Revised
14
15 183 Atlanta criteria (20), with an unknown origin after standard diagnostic work-up, according to the 2013
16
17 184 International Association of Pancreatology/American Pancreatic Association (IAP/APA) evidence-
18
19 185 based guidelines on management of acute pancreatitis (11). The diagnostic modalities that constitute
20
21 186 standard diagnostic work-up are listed in table 1 and additional file 1. The diagnostic tests as laid out
22
23 187 in table 1 are to be performed in all subjects and these tests cannot show any signs of an etiology in
24
25 188 all subjects. Potential etiologies and their definitions are listed in table 2 and additional file 1.
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32 190 Eligibility criteria

34 191 The inclusion criteria are:

- 36
37 192 1. Patients of 18 years or older
38
39 193 2. First episode of presumed IAP after standard diagnostic work-up, as defined by the IAP/APA
40
41 194 evidence-based guidelines on management of acute pancreatitis (11)
42
43 195 3. Informed consent for participation
44
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49 197 The exclusion criteria are:

- 51
52 198 1. Known etiology
53
54 199 2. Chronic pancreatitis, as defined by the M-ANNHEIM criteria (21)
55
56 200 3. Recurrent pancreatitis
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3 201 4. Altered anatomy which prohibits the endosonographer from visualizing the gall bladder, bile
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5 202 ducts, pancreas or pancreatic duct via EUS (e.g. gastric bypass surgery)
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7 203 5. Diagnostic EUS aimed to determine etiology before inclusion
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12
13 205 Endoscopic ultrasonography

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15 206 EUS will be performed in routine clinical practice by an endosonographer. Use of linear or radial EUS
16
17 207 will be at the discretion of the endosonographer. All Dutch endosonographers are trained to perform
18
19 208 EUS according to the technique of Hawes and Fockens (22).
20
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23 209 The endosonographer will systematically report, using a standardized Case Report Form (CRF),
24
25 210 the experience of the endosonographer, visualization of anatomical structures (i.e. gall bladder,
26
27 211 common bile duct and pancreatic duct), presence of local complications of acute pancreatitis,
28
29 212 characteristics of biliary etiology (i.e. gallstones, microlithiasis and/or biliary sludge), characteristics of
30
31 213 chronic pancreatitis, presence of (a) pancreatic or peri-ampullary benign or malignant tumor(s),
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33 214 characteristics of auto-immune pancreatitis, anatomic variations (e.g. pancreas divisum) or other
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35 215 anomalies (e.g. cholecystitis, vascular, renal, splenic or hepatic anomalies or ascites), and performance
36
37 216 of fine needle aspiration or fine needle biopsy. Additionally, the type of endoscope, use of sedation,
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39 217 procedure related complications and results of the fine needle aspiration or biopsy will be
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41 218 systematically recorded by the study coordinator in a separate CRF.
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49 220 Primary outcome measure

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51 221 The primary outcome measure is the number and ratio of patients with presumed IAP in whom EUS
52
53 222 detects a cause for the pancreatitis episode.
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56 223 A positive EUS is defined as an EUS during which a definitive cause for the acute pancreatitis
57
58 224 episode has been found; or during which abnormalities are visualized constituting a definitive cause,
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225 after obtaining tissue and pathological examination. An overview of the exact findings scored as
226 positive imaging is provided in table 3.

227 If during EUS pancreatic abnormalities are found, yet not enough to make a certain diagnosis
228 of chronic pancreatitis according to the M-ANNHEIM classification (21), this imaging is considered to
229 be negative, even though it did show abnormalities. This approach is chosen because the aim of this
230 study is to determine the rate of which EUS can find a cause for the presumed IAP episode. For the
231 same reason, report of an anatomical abnormality during EUS after a first episode of acute pancreatitis
232 is not scored as positive imaging as pancreatic morphological changes are very common in IAP and not
233 necessarily clinically relevant, as is elaborated on in the discussion (23).

234

235 Secondary outcome measures

236 The secondary outcome measures are recurrence rate of acute pancreatitis, severity of recurrent
237 pancreatitis (20), readmission, performance of additional invasive procedures (e.g. cholecystectomy,
238 endoscopic sphincterotomy), complications of EUS and of additional interventions, according to the
239 Clavien-Dindo classification (24), length of hospital stay, quality of life, mortality and costs. Relevant
240 definitions are reported in Additional File 2.

241

242 Sample size calculation

243 The sample size calculation was based on the primary outcome measure, diagnostic yield of EUS. Based
244 on two previous studies reporting yield in patients with a first episode of presumed IAP (25, 26),
245 adjusted for the PICUS study criteria for inclusion (i.e. requiring negative imaging after clinical
246 recovery) and for positive imaging (i.e. excluding pancreas divisum as etiology), diagnostic yield was
247 assumed to be 30%. Using a two-sided significance level (α) of 0.05, a power ($1 - \beta$) of 80%, 95 patients
248 are needed to attain a 95% confidence interval (CI) with a range smaller than 10% above and below

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3 249 the assumed yield of 30% (95% CI: 20.8, 39.2). Assuming a drop-out rate of 10%, a total of 106 patients
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5 250 will be included (27). The sample size was calculated using the software programs RStudio (28) and
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7 251 nQuery (29).
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12 13 253 Follow-up

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16 254 Data from patient records on primary and secondary outcome measures will be collected until 1 year
17
18 255 after inclusion. Outpatient care and follow-up after the EUS is at the discretion of the treating
19
20 256 physician, but an outpatient clinic visit after EUS to discuss the results of the EUS and potential
21
22 257 subsequent appropriate treatment can be considered standard care.
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26 258 In case of biliary disease, the patient will be considered for endoscopic retrograde
27
28 259 cholangiopancreatography (ERCP) with sphincterotomy when choledocho(-micro-)lithiasis or sludge
29
30 260 in the common bile duct is present, and cholecystectomy, as is standard care for biliary pancreatitis. A
31
32 261 (secretin-enhanced) MRCP will be recommended, if not performed earlier, if a patient is readmitted
33
34 262 for a recurrent episode of acute pancreatitis after a negative EUS for etiology, in order to rule out
35
36 263 structural anomalies such as pancreas divisum. This is in accordance with current guidelines (11).
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40 264 Patients will be asked to fill out the Short Form-36 questionnaire in the validated Dutch
41
42 265 translation on day 3 after inclusion, after 6 months and after 1 year. This questionnaire in both English
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44 266 and Dutch is included in additional file 3.
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48 49 50 268 Statistical aspects

51
52 269 All included subjects will be evaluated for primary and secondary endpoints until 1 year after inclusion.
53
54 270 The primary analysis will be based on intention-to-treat principles. For exploratory reasons a per-
55
56 271 protocol analysis will be performed too.
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3 272 The intention-to-treat population comprises all patients included in the study, regardless of
4
5 273 adherence to study protocol. The per-protocol population is the subset of included patients who were
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7 274 treated with the guidelines of the protocol (i.e. meeting all eligibility criteria including all of the
8
9
10 275 diagnostic tests required for the diagnosis of IAP, undergoing EUS as described in the “Endoscopic
11
12 276 ultrasonography section”). A tabular listing of all patients excluded from the intention-to-treat
13
14 277 population will be provided together with the reasons for exclusion.
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16

17 278 All analyses will be performed in SPSS for Microsoft Windows. All data handling and analysis
18
19 279 will be saved in a syntax-file. Results will be presented with all centers combined. A two-tailed p-value
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21
22 280 of < 0.05 is considered statistically significant.
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28 282 ***Baseline variables***

29
30 283 The reported baseline characteristics consist of age, sex, body mass index (BMI), previous
31
32 284 cholecystectomy, nicotine and alcohol use, severity of pancreatitis, length of hospital stay, amylase,
33
34 285 lipase, C-reactive protein, alanine transaminase, calcium, albumin and triglycerides levels in blood
35
36 286 serum on admission, imaging modalities before EUS and their findings. Baseline characteristics of EUS
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39 287 will include timing of EUS, experience of endosonographer and type of sedation and type of endoscope
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41 288 used. Data will be presented in percentages or as mean with standard deviation, or in case of a skewed
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43 289 distribution as median with interquartile range (IQR).
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50 291 ***Primary outcome measure: etiology detection rate***

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52 292 Overall detection rate of an etiology for the episode of acute pancreatitis will be presented as
53
54 293 percentage with a 95% CI. Predefined subgroup analyses will be made for patients with and without
55
56 294 obesity (cut-off at a BMI of 30), a previous cholecystectomy, alcohol use and local complications from
57
58 295 the IAP episode. A subgroup analysis will also be made for patients with a transabdominal ultrasound
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3 296 as imaging after clinical recovery and with magnetic resonance imaging (MRI) or MRCP as imaging after
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5 297 clinical recovery. Finally, a subgroup analysis will be made for EUS performed by endosonographers
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7 298 with and without extensive experience (cut-off at 400 endosonographies performed), use of linear or
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10 299 radial scope and type of sedation used. In subgroup analyses, the Chi-square test or the Fisher's exact
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12 300 test will be used, as appropriate, to compare etiology detection rate between subgroups. In subgroup
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14 301 analyses, comparability between groups regarding baseline variables will be checked. If the subgroups
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16 302 differ statistically significantly in one or more baseline variables, this will be corrected in a logistic
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18 303 regression analysis.
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25 305 ***Secondary outcome measures***

26
27 306 Secondary outcome measures will be described as percentages with 95% CI, as mean with standard
28
29 307 deviation or median with IQR, as appropriate.
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33 308 For recurrence rate, subgroup analyses will be made for patients with a positive and negative
34
35 309 EUS, and in patients with a positive EUS, for patients who were and were not treated adequately. The
36
37 310 same subgroup analyses as in the primary outcome measure, will also be applied on the recurrence
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39 311 rate. The Chi-square test or the Fisher's exact test will be used for comparison between subgroups, as
40
41 312 appropriate.
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45 313 For quality of life, subgroup analyses will be made for baseline versus follow-up quality of life
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47 314 and for patients with a positive and negative EUS, and with and without pancreatitis recurrence during
48
49 315 follow-up. The (un-)paired T-test, Wilcoxon signed rank test or the Mann-Whitney U test will be used
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51 316 for comparisons between subgroups, as appropriate.
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3 318 **Cost analysis**
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5 319 The cost analysis will comprise direct medical costs, which are generated by healthcare utilization and
6
7 320 include hospital admission periods and therapeutic and diagnostic procedures (30). Estimates of unit
8
9
10 321 costs will be based on Dutch reference data from the cost guide of the Dutch Health Council (31). If
11
12 322 this guide is an inappropriate determination of unit costs, the costs will be based on data provided by
13
14 323 two hospital administrations (one university center and one general hospital) to account for the actual
15
16 324 input of personnel, material and overhead over hospital resources used. Cost calculations will be used
17
18 325 to determine cost of interventions (surgical, endoscopic or radiological) and diagnostic imaging. The
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20
21 326 cost analysis will be reported separately from the main study manuscript.
22
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27 328 **Patient and public involvement**
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29 329 The patient advocacy organization '*Alveeskliervereniging Nederland*' was involved in the design of the
30
31 330 PICUS study. The experience of the patient advocacy organization with IAP and participation in
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33 331 scientific research has driven the research question and design of the study with regards to patient
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35 332 burden. The patient advocacy organization will also be involved in the dissemination and
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37 333 implementation of the study results.
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41 334 All patients eligible for participation will be asked to give written informed consent.
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50 337 **Ethics and dissemination**
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52 338 The PICUS study is conducted according to the principles of the Declaration of Helsinki (October 2013)
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54 339 and to the Guideline for Good Clinical Practice by the International Council for Harmonization
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57 340 (November 9 2016).
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3 341 The need for ethical approval was waived by the Medical Ethics Review Committee of the
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5 342 Academic Medical Center on May 28, 2018 (W18_161 # 18.199), by the Medical Research Ethics
6
7 343 Committee of the University Medical Center Utrecht on July 04, 2018 (18-469), by the Research Ethics
8
9 344 Committee of Radboud university medical center on July 23, 2018 (2018-4520), by the Medical Ethics
10
11 345 Review Committee of the Erasmus Medical Center on July 30, 2018 (MEC-2018-1293) and by the
12
13 346 Medical Ethics Review Committee of the Maastricht University Medical Center on September 7, 2018
14
15 347 (2018-0685). Before start of inclusion, local board approval will be obtained in all participating centers.
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19 348 The results of the PICUS study will be submitted for publication in an international peer-
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21 349 reviewed scientific journal, regardless of study outcomes.
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30 352 Discussion

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33 353 Previous research has suggested that EUS might be beneficial in the detection of an etiology in
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35 354 presumed IAP. However, data lacks on the efficacy of routine EUS in patients with a first episode of
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37 355 presumed IAP, after repeat imaging after clinical recovery is negative for an etiology. The PICUS study
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39 356 aims to determine whether routine EUS is warranted in a first episode of acute pancreatitis where no
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41 357 cause could be uncovered after complete standard diagnostic work-up.
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45 358 Currently, guidelines do not clearly define criteria for biliary origin (11). However, it is generally
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47 359 agreed upon that cholelithiasis, microlithiasis or biliary sludge constitute biliary etiology. Several
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49 360 previous studies have shown an association between elevated ALT levels and acute biliary pancreatitis
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51 361 (32-35), with a positive predictive value of 85% for an ALT > 150 U/L within 48 hours after onset of
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53 362 symptoms (11, 32, 33, 35). Therefore, an elevated blood serum ALT level at admission is considered to
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55 363 entail a high probability of biliary etiology, and pancreatitis with an elevated ALT is treated as being of
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57 364 biliary origin (32-34, 36). However, the majority of current literature on EUS did not exclude patients
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3 365 based on ALT level at admission (15, 25, 26, 32, 37-46). As these patients have a higher a priori chance
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5 366 of confirmation of biliary etiology on EUS, the etiology detection rate of EUS might be overestimated
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7 367 in these studies. In PICUS, biliary etiology is defined as either the signs of cholelithiasis, microlithiasis
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10 368 or biliary sludge on transabdominal ultrasonography, or transient elevation of the blood serum ALT
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12 369 level of more than twice the upper limit of normal at admission in the absence of ALT elevating
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14 370 comorbidity. By only including patients with normal or slightly elevated ALT levels at admission, the
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16 371 etiology detection rate as reported in PICUS will reflect the detection rate in patients who are truly
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18 372 considered as having presumed IAP after standard diagnostic work-up.
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21 373 Current guidelines advise a repeat transabdominal ultrasound after clinical recovery in the
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23 374 work-up of presumed IAP because the index transabdominal ultrasound is less sensitive during the
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25 375 acute phase of pancreatitis. The subpar visualization of gall bladder, bile ducts and pancreas is often
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27 376 due to excessive amounts of air in the intestines caused by pancreatitis-induced ileus and/or
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29 377 suboptimal cooperation of painful patients (47). After the first episode of acute pancreatitis, repeating
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31 378 a transabdominal ultrasound may be able to detect biliary stones where it could not during index
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33 379 admission (48). Of the current literature on EUS in IAP, however, only a minority of studies included
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35 380 repeat imaging in the diagnostic work-up before EUS (15, 40, 41, 43). Previous research has shown that
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37 381 a repeat transabdominal ultrasound has a diagnostic yield of 20% in patients with a first episode of IAP
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39 382 (49). Omitting repeat imaging from diagnostic work-up before EUS may lead to an overestimation of
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41 383 the diagnostic yield of EUS. In PICUS, all patients are required to undergo imaging after clinical
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43 384 recovery, i.e. transabdominal ultrasound or MRI/MRCP. Computed tomography (CT) is not considered
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45 385 sufficient imaging as biliary disease, the most common underlying etiology in presumed IAP, cannot
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47 386 always be adequately detected using CT.
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54 387 It is well documented that the overall diagnostic yield of EUS in patients with recurrent
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56 388 pancreatitis is superior to the diagnostic yield of both secretin-enhanced MRCP (s-MRCP) and non-
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58 389 secretin-enhanced MRCP (18, 44, 46, 50). In the subgroup of patients with a pancreas divisum,
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3 390 however, s-MRCP is considered to be superior in diagnostic yield to both EUS and MRCP (18). The role
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5 391 of pancreas divisum in the etiology of pancreatitis is unclear. Epidemiological studies have shown that
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7 392 the prevalence of pancreas divisum in the general population is equal to the prevalence in patients
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9 393 with presumed IAP (23). In patients with a pancreas divisum and acute pancreatitis, potentially other
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11 394 disease modifying factors add to the occurrence of pancreatitis, such as increased sensitivity to toxins
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13 395 or genetic susceptibility. Because of this ambiguity, pancreas divisum in patients with a first episode
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15 396 of acute pancreatitis is mostly left untreated in clinical practice. However, if patients with a pancreas
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17 397 divisum present with multiple episodes of presumed IAP, the divisum is often considered to be related
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19 398 to the pancreatitis and is subsequently treated, often with ERCP with endoscopic sphincterotomy,
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21 399 although evidence supporting this practice is limited (23). Because of both the diagnostic superiority
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23 400 of EUS in recurrent pancreatitis as well as the lack of clinical consequences of (s-)MRCP in patients with
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25 401 a first episode of pancreatitis, EUS is preferred to (s-)MRCP as the first choice for additional diagnostic
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27 402 testing for etiology in patients with presumed IAP (18, 44, 46, 50). Subsequently, current guidelines
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29 403 advise performing MRCP in case of recurrent IAP after EUS fails to determine an etiology (11).
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31 404 Therefore, in PICUS, we have chosen not to systematically include (s-)MRCP in the diagnostic work-up
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33 405 before EUS of first episode IAP.
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40 406 Current guidelines advise consideration of EUS after a first or second attack of IAP (11).
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42 407 However, there is a paucity of evidence on the efficacy of EUS in first episode IAP. Three previous
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44 408 studies prospectively reported on EUS in patients with first episode IAP (25, 26, 38). However, in these
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46 409 studies, patients were not excluded based on liver enzymes abnormalities suggestive of biliary disease
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48 410 and no repeat imaging after clinical recovery was performed. PICUS will be the first prospective cohort
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50 411 study in which EUS will be performed in patients with a first episode of IAP after complete standard
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52 412 diagnostic work-up before EUS according to current guidelines (11).
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56 413 A diagnostic yield of 10% for any etiology will be considered reasonable to justify incorporating
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58 414 routine EUS after a first episode of presumed IAP. This cut-off value was determined during a
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3 415 multidisciplinary meeting of the Dutch Pancreatitis Study Group, which included the principal
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5 416 investigators of several trials being executed by the Dutch Pancreatitis Study Group. Considering the
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7 417 expectation that the majority of uncovered etiologies by EUS will be treatable (e.g. biliary disease) and
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9 418 adequate treatment could prevent pancreatitis recurrence, while in a minority of uncovered etiologies
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11 419 diagnosis before progression of disease might be crucial for prognosis (e.g. malignancy), a positive
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13 420 result in 10% of patients was deemed sufficient to warrant routine EUS after a first episode of
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15 421 presumed IAP.
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19 422 In conclusion, the PICUS study is the first prospective cohort study of patients with a single
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21 423 episode of presumed IAP after complete standard diagnostic work-up (including exclusion based on
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23 424 blood serum ALT and imaging after clinical recovery). The results of the PICUS study will establish
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25 425 whether routine EUS should be incorporated in the guidelines for standard diagnostic work-up after a
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27 426 first episode of presumed IAP.
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39
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604 Author Statement

605 Authors' contributions

606 DSU drafted the manuscript. HCT, RCV, SAB, MGB and JEvH co-authored the writing of the manuscript.
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610 RLJvW and BJW critically assessed the study design, during several meetings, and edited the
611 manuscript. All authors read and approved the final manuscript.

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4

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6
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8
9 616 design, implementation and conduct of the study, as well as on collection, analysis and interpretation
10
11 617 of data, construction of the manuscript and decision to publish.
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18 619 Competing interests statement
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20 620 The authors declare that they have no competing interests.
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26 622 Data Availability Statement
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29 623 The datasets used and/or analyzed during the current study are available from the corresponding
30
31 624 author on reasonable request.
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40 627 Figure legend
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42 628 Figure 1: Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP =
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44 629 magnetic resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic
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47 630 ultrasonography.
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634 Table 1

Standard diagnostic work-up	
<i>Detailed personal and family history, including questions on:</i>	Alcohol use
	Recent ERCP
	Recent start or changes in use of drugs associated with acute pancreatitis
	Recent major abdominal trauma
	Recent abdominal surgery
	Familial and hereditary pancreatitis
	Cystic fibrosis-related pancreatitis
<i>Laboratory tests, including:</i>	Blood serum triglycerides level
	Blood serum calcium level, corrected for the blood serum albumin level
	Blood serum ALT level on admission
<i>Imaging:</i>	Transabdominal ultrasound, MRI or MRCP after clinical recovery

635 **Table 1: Standard diagnostic work-up** Standard diagnostic work-up according to the 2013 IAP/APA evidence-based guideline
 636 on management of acute pancreatitis. A listing of the drugs considered to be associated with acute pancreatitis are listed in
 637 additional file 1. ERCP = endoscopic retrograde cholangiopancreatography; ALT = alanine aminotransferase; MRI = magnetic
 638 resonance imaging; MRCP = magnetic resonance cholangiopancreatography.

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645 Table 2

Etiology	Definition
Alcohol	> 4 units of alcohol in the 24 hours prior to start of abdominal complaints (51-53)
Biliary disease	<ol style="list-style-type: none"> <li data-bbox="485 501 1394 674">1. A transient elevated ALT level of >2 times the upper limit of normal at diagnosis of acute pancreatitis, in the absence of other ALT elevating comorbidity (34), OR <li data-bbox="485 730 1394 763">2. Gallstones, microlithiasis and/or biliary sludge, OR <li data-bbox="485 819 1394 931">3. A dilated CBD of >8 mm in patients <76 years or >10 mm in patients >75 years at diagnosis of acute pancreatitis (36)
Cystic fibrosis	history of cystic fibrosis in the absence of another origin (54)
Familial	two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis (55-57)
Hereditary	mutation in the PRSS1, SPINK1, CFTR, CTSC, CLDN2 or CPA1 gene, or direct family member (parents, children, siblings) with one or more of the above mentioned mutations and at least one direct family member who has (had) acute or chronic pancreatitis (57, 58)
Hypercalcemia	blood serum calcium level ≥ 12 mg/dl (3 mmol/l), corrected for serum albumin level, as first measured during admission (59)
Hypertriglyceridemia	blood serum triglyceride level of ≥ 1000 mg/dl (11.2 mmol/l) under fasting conditions, as first measured during admission (60)
Medication	use of drug(s) listed in additional file 1, which has or have been started or increased in dosage within a reasonable temporal sequence, in principle 1

	month before onset of pancreatitis, and has or have a positive dechallenge (a drug reaction that is confirmed by stopping the drug) (61, 62)
Neoplasm	Known hepatopancreatobiliary malignancy or known malignancy with metastases causing obstruction of the pancreatic duct (63)
ERCP	ERCP within 24 hours before diagnosis of pancreatitis (64)
Surgical	abdominal surgery within 24 hours prior to diagnosis of pancreatitis (65)
Trauma	typical blunt trauma to the upper abdomen and pancreatic trauma visible on imaging (66)

646 **Table 2: potential etiologies and their definitions** Potential etiologies and their definitions. Side branch or mixed type
647 *intraductal papillary mucinous neoplasms without dilatation of the pancreatic duct and pancreas divisum will not be*
648 *considered to be a causative factor for the pancreatitis episode. If imaging is not able to discriminate between gall bladder*
649 *polyps or concrements, lesions smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm,*
650 *irrespective of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and these patients*
651 *will be excluded from PICUS. ALT = alanine transaminase. CBD = common bile duct. ERCP = endoscopic retrograde*
652 *cholangiopancreatography.*

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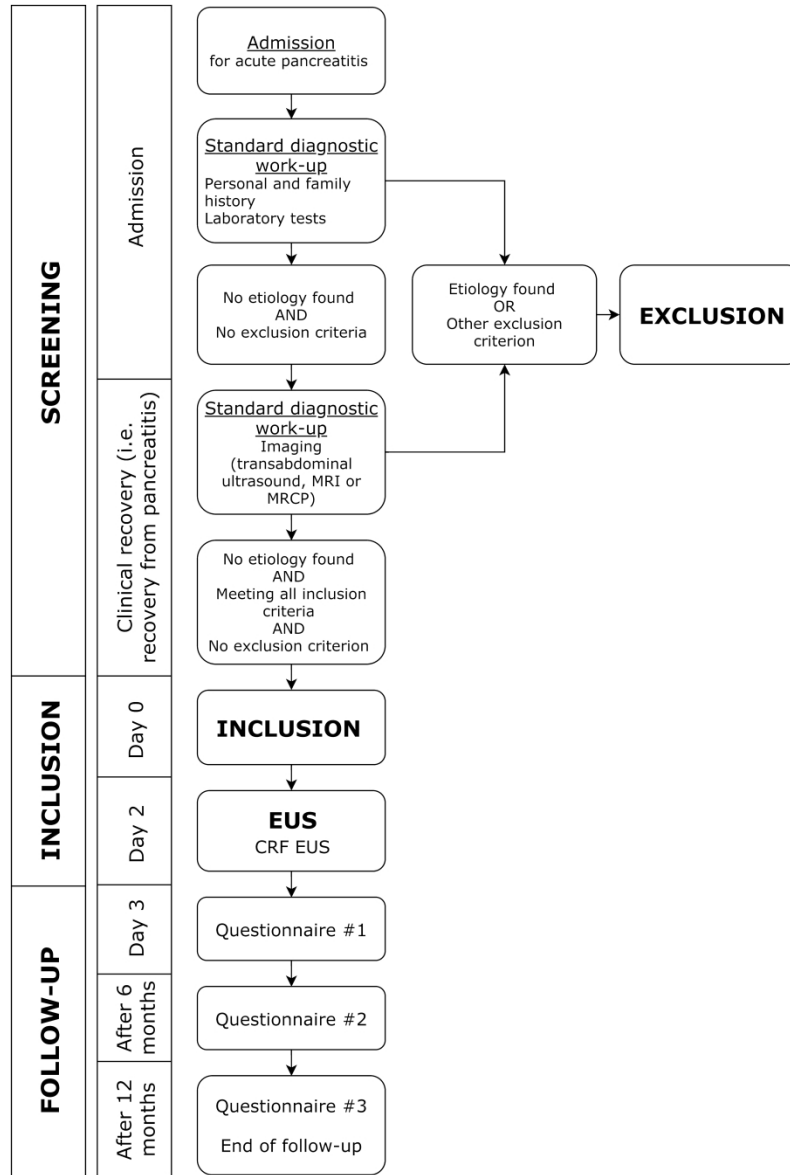
659

660 Table 3

<i>Biliary pancreatitis</i>	Presence of biliary stones, microlithiasis, or sludge
	Widened CBD, >8 mm in patients <76 years, or >10 mm in patients >75 years, in the absence of other CBD dilating factors (e.g. opioid use, distal stenosis, obstruction of external compression of CBD or papilla (67))
<i>Chronic pancreatitis</i>	Pancreatic calcifications
	> 4 of the following abnormal features of the pancreas: <ol style="list-style-type: none"> 1. Enlarged gland size 2. Cysts 3. Echo-poor lesions (focal areas of reduced echogenicity) 4. Echo-rich lesions (> 3 mm in diameter) 5. Accentuation of lobular pattern 6. Increased duct wall echogenicity 7. Irregularity of the main pancreatic duct 8. Dilation of the main pancreatic duct > 3.5 mm (68) 9. Visible side branches 10. Calcifications of the pancreatic duct
<i>Neoplasms</i>	Definitive diagnosis of pathological tissue after histological or cytological evaluation of specimen of an anomaly observed during EUS, e.g. hyperplastic or malignant tissue, or auto-immune inflammatory disease
	Main duct IPMN or mixed type IPMN causing dilatation of the pancreatic duct

661 **Table 3: positive imaging** Definition of positive imaging. For each diagnosis, presence of one of the separately mentioned
662 abnormalities is required to be considered as positive imaging. Specimen is not required to be obtained during EUS. Anatomical
663 anomalies (e.g. divisum) are not considered a certain etiology in first episode IAP and therefore not considered as positive
664 imaging. CBD = common bile duct. EUS = endoscopic ultrasonography. IPMN = intraductal papillary mucinous neoplasm.

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Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP = magnetic resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic ultrasonography.

105x154mm (1200 x 1200 DPI)

Additional file 1: Table S1 Drugs associated with acute pancreatitis

Drugs associated with acute pancreatitis				
Acetaminophen	Cisplatin	Hydrochlorothiazide	Methyldopa	Pentavalent antimony compounds
Asparaginase	Cytarabine	Interferon alpha	Metronidazole	
Azathioprine	Didanosine	Itraconazole	Octreotide	Phenformin
Bortezomib	Enalapril	Lamivudine	Olanzapine	Simvastatin
Capecitabine	Erythromycin	Mercaptopurine	Opiates	Steroids
Carbamazepine	Estrogens	Mesalazine	Oxyphenbutazone	Sulfasalazine
Cimetidine	Furosemide	Olsalazine	Pentamidine	co-trimoxazole

Drugs with a definite association with acute pancreatitis (1, 2)

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1 Additional file 2: Relevant definitions

2 Acute pancreatitis: an acute inflammation of the pancreatic parenchyma, diagnosed when at least two
3 of the three following characteristics are present (1):

- 4 1. Clinical features of acute pancreatitis, such as upper abdominal pain
- 5 2. Elevated serum amylase or lipase levels of at least three times the upper limit of normal (ULN)
- 6 3. Signs of acute pancreatitis on imaging

7 Note: no value of the required serum amylase or lipase level is provided as every participating center
8 has a local laboratory, which is why each center may use different normal range values.

9
10 Idiopathic acute pancreatitis is considered to be present if no etiology is found in standard work-up,
11 according to the IAP/APA evidence-based guidelines on management of acute pancreatitis (2), which
12 comprises at least the following tests:

- 13 1. A detailed personal and family history, including questions on:
 - 14 a. Alcohol use
 - 15 b. Recent endoscopic retrograde cholangiopancreatography (ERCP)
 - 16 c. Recent start of or changes in use of drugs associated with acute pancreatitis
 - 17 d. Recent major abdominal trauma
 - 18 e. Recent abdominal surgery
 - 19 f. Familial pancreatitis
 - 20 g. Hereditary pancreatitis

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3 21 h. Cystic fibrosis related pancreatitis
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6 22 2. Laboratory tests, including:
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9 23 a. Blood serum triglycerides level on admission
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12 24 b. Blood serum calcium level, corrected for the serum albumin level, on admission
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15 25 c. Blood serum alanine transaminase (ALT) level on admission
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18 26 3. Imaging via transabdominal ultrasound, magnetic resonance imaging (MRI) or magnetic
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20 27 resonance cholangiopancreatography (MRCP) after clinical recovery
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23 28 Note: side branch or mixed type intraductal papillary mucinous neoplasms (IPMN) without dilatation
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25 29 of the pancreatic duct will not be considered to be a causative factor for the pancreatitis episode.
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28 30 Note: if the imaging is not able to discriminate between gall bladder polyps or concrements, lesions
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30 31 smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm, irrespective
31
32 32 of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and
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34 33 will be excluded from PICUS.
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40 35 Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when biliary
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42 36 etiology is not demonstrated by standard work-up and the patient has indicated (either by direct or
43
44 37 indirect personal history or by findings during physical examination) to have drunk at least five units of
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46 38 alcohol in the 24 hours prior to start of abdominal complaints (or in asymptomatic acute pancreatitis:
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48 39 prior to diagnosis) (3-5)
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3 42 Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one
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5 43 of the following features is present:

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8 44 1. A transient elevated ALT level of more than two times the ULN at diagnosis of acute
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10 45 pancreatitis, in the absence of ALT elevating comorbidity (6)
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13 46 2. Signs of presence of gallstones, microlithiasis or sludge on imaging, defined as follows:
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16 47 a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus
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18 48 cysticus, intrahepatic bile ducts or in the common bile duct (CBD), and/or
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21 49 b. A CBD of more than eight mm in patients 75 years old or younger or more than ten
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23 50 mm in patients older than 75 years at diagnosis of acute pancreatitis (7)

24
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26 51 Note: no value of the required serum ALT level is provided as the normal range values depend on the
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28 52 sex of the patient and as every participating center has a local laboratory, which is why each center
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30 53 may use different normal range values.

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37 55 Chronic pancreatitis: a chronic inflammation of the pancreatic parenchyma, defined as typical clinical
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39 56 history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary
40
41 57 painless pancreatitis) and one or more of the following (8):

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43
44 58 1. Pancreatic calcifications
- 45
46
47 59 2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features
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49 60 on transabdominal ultrasound, computed tomography (CT) or MRI/MRCP, according to the
50
51 61 Cambridge classification (9):
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54 62 a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of
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56 63 the duct wall (mandatory)
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59 64 b. Pancreatic enlargement
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- 65 c. Cavities
 - 66 d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
 - 67 e. Focal acute pancreatitis
 - 68 f. Parenchymal heterogeneity
 - 69 g. Irregularities of pancreatic head or body contour
- 70 3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features
- 71 on endoscopic ultrasonography (EUS):
- 72 a. Enlarged gland size
 - 73 b. Cysts
 - 74 c. Echo-poor lesions (focal areas of reduced echogenicity)
 - 75 d. Echo-rich lesions (more than three mm in diameter)
 - 76 e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by
 - 77 hyperechoic strands)
 - 78 f. Increased duct wall echogenicity
 - 79 g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
 - 80 h. Dilation of the main pancreatic duct
 - 81 i. Visible side branches (e.g., with dilation)
 - 82 j. Calcification (of the pancreatic duct)
- 83 4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly
- 84 reduced by enzyme supplementation
- 85 5. Typical histology of an adequate histological specimen

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3 86 Note: during initial diagnostic work-up during admission 'marked and persistent exocrine insufficiency'
4
5 87 cannot be evaluated properly. Therefore this part of the definition of chronic pancreatitis will not be
6
7 88 applicable during standard work-up. However, if the patient does show marked and persistent
8
9 89 exocrine insufficiency during follow-up (either during the outpatient clinic visit after repeat
10
11 90 transabdominal ultrasound or after the EUS), this will be considered to be diagnostic for chronic
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13 91 pancreatitis. The same is applicable for histology of an adequate histological specimen: this is not part
14
15 92 of standard work-up, however, if a typical histological specimen is obtained during follow-up, this will
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17 93 be considered to be diagnostic for chronic pancreatitis.
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24 95 Clinical recovery from acute pancreatitis: resolution of pancreatic inflammation, present when one of
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26 96 the following criteria is met:

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29 97 1. Discharge from the hospital
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32 98 2. Normal inflammation parameters in laboratory tests
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35 99 3. No signs of pancreatic inflammation on imaging
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41 101 Cystic fibrosis: an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in
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43 102 defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride
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45 103 greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both (10).
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51 105 Cystic fibrosis related pancreatitis: pancreatitis caused by defective ductular and acinar pancreatic
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53 106 secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis
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55 107 in the absence of another origin (10).
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3 109 Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that
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5 110 is greater than would be expected by chance alone, given the size of the family and the standardized
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7 111 incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who
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9 112 have two or more direct blood-related family members (parents, children or siblings) who have had an
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11 113 episode of acute pancreatitis (11-13).

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18 115 Fever: a body temperature of 38.5°C or higher.

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24 117 Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the
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26 118 pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in
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28 119 an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the
29
30 120 PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTSC gene, the CLDN2 gene or the CPA1 gene, or if
31
32 121 the patient has a direct family member (parents, children, siblings) with one or more of the above
33
34 122 mentioned mutations and has at least one direct family member who has had an episode of acute
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36 123 pancreatitis or has chronic pancreatitis (13, 14).

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43 125 Hypercalcemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs
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45 126 of a biliary pancreatitis are found in standard work-up and the patient has a blood serum calcium level
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47 127 of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during
48
49 128 admission (15).

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3 131 Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if
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5 132 a biliary etiology is not demonstrated by standard work-up and the patient has a blood serum
6
7 133 triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured
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9 134 during admission (16).
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15 136 Hypothermia: a body temperature of 35.9°C or lower.
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21 138 Infected (extra)pancreatic necrosis: presence of microorganisms in (extra-)pancreatic necrosis,
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23 139 confirmed by a positive culture obtained by means of fine needle aspiration or from the first drainage
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25 140 procedure or necrosectomy, the presence of gas in the (extra-)pancreatic collection on CT, or the
26
27 141 presence of clinical signs of persistent sepsis or progressive clinical deterioration despite maximal
28
29 142 support on the intensive care unit (ICU) without other causes for infection (ruled out should be:
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31 143 pneumonia, urinary tract infection, wound infection, endocarditis, abdominal sepsis or any other
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33 144 infection which could be suspected based on the individual patient's clinical presentation) (17).
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39 146 Medication associated pancreatitis: acute pancreatitis is considered to be caused by drugs when a
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41 147 biliary cause is not demonstrated by standard work-up, the patient uses one or multiple drug(s) listed
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43 148 in table S1 in additional file 1, the drug has been started or increased in dosage within a reasonable
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45 149 temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive
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47 150 dechallenge (a drug reaction that is confirmed by stopping the drug) (18, 19).
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54 152 Microlithiasis: stones or concrements, smaller than four mm, in the gall bladder or the bile ducts (20).
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3 154 Murphy's sign: the phenomenon where compression of the right upper quadrant causes the patient
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5 155 to catch their breath due to pain when taking a deep breath (21).
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11 157 Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two
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13 158 separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one
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15 159 main duct (of Wirsung) (22).
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21 161 Positive imaging: positive imaging is defined as imaging during which a definitive cause for the acute
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23 162 pancreatitis episode can be found; or during which abnormalities are visualized constituting a
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25 163 definitive cause, after obtaining tissue and pathological examination. So, if during EUS ductal
26
27 164 abnormalities are found, yet not enough to make a certain diagnosis of chronic pancreatitis according
28
29 165 to the M-ANNHEIM classification (8), this imaging is considered to be negative, even though it did show
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31 166 abnormalities. This approach is chosen because the aim of this study is to determine the rate of which
32
33 167 EUS can find a causative factor for a previous acute pancreatitis episode. For the same reason, finding
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35 168 of an anatomical abnormality after a first episode of acute pancreatitis is not scored as positive
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37 169 imaging. An overview of the exact findings scored as positive imaging is provided in table 3 of the main
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39 170 manuscript.
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47 172 Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic
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49 173 injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24
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51 174 hours of an ERCP without indications of another origin (23).
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3 176 Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas,
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5 177 diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of
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7 178 indications for another origin (24).
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13 180 Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen,
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15 181 diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic
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17 182 trauma is visible on imaging (25).
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23 184 Recurrence rate: the risk of a recurrent episode of acute pancreatitis.
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29 186 Sludge: solid material which results from the slow settling of particles dispersed in bile (20).
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3 197 Standard work-up:
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6 198 1. A detailed personal and family history, including questions on:
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9 199 a. Alcohol use
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12 200 b. Recent ERCP
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15 201 c. Recent start of or changes in use of drugs associated with acute pancreatitis
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18 202 d. Recent major abdominal trauma
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21 203 e. Recent abdominal surgery
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24 204 f. Familial pancreatitis
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27 205 g. Hereditary pancreatitis
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30 206 h. Cystic fibrosis related pancreatitis
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32 207 2. Laboratory tests, including:
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35 208 a. Blood serum triglycerides level, first measured during admission
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38 209 b. Blood serum calcium level, corrected for the serum albumin level, first measured
39 during admission
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43 211 c. Blood serum ALT level on admission
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46 212 3. Imaging via transabdominal ultrasound, MRI or MRCP after clinical recovery
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52 214 Biliary events: acute cholecystitis; biliary colic's requiring readmission; biliary pancreatitis; cholangitis;
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54 215 or obstructive choledocholithiasis needing ERCP.
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3 217 Acute cholecystitis: an acute inflammation of the gall bladder, diagnosed when one item in A, B and C

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5 218 is present:

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8 219 A) Local signs of inflammation

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11 220 1. Murphy's' sign, or

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14 221 2. Right upper abdominal quadrant mass, pain or tenderness

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17 222 B) Systemic signs of inflammation

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20 223 1. Fever or hypothermia, or

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23 224 2. Elevated C-reactive protein (CRP), or

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26 225 3. Elevated white blood cell count

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29 226 C) Imaging findings characteristic of acute cholecystitis (26, 27)

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31 227 Note: acute cholecystitis and cholangitis (see definition below) are defined according to the Tokyo
32
33 228 classification which defines fever as a body temperature of 38°C or higher; however, fever will be
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35 229 defined in this study as hyperthermia of 38.5°C or higher and hypothermia will be added as a systemic
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37 230 sign of inflammation, as this more accurately reflects clinical practice in the Netherlands.

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44 232 Biliary colic: upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30

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46 233 minutes, often associated with restlessness (28).

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3 238 Cholangitis: an inflammation of the bile duct(s), diagnosed when one item in each of the following
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5 239 categories is present:

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8 240 1. Systemic inflammation

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11 241 a. Fever, hypothermia and/or shaking chills

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13
14 242 b. Laboratory data: evidence of inflammatory response (abnormal white blood cell
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16 243 counts (defined as smaller than 4,000/ μ l or larger than 10,000/ μ l), increase of serum
17
18 244 CRP levels (defined as 1 mg/dl or higher), and other changes indicating inflammation)

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21 245 2. Cholestasis

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24 246 a. Jaundice (defined as a total bilirubin of 2 mg/dl or higher)

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26
27 247 b. Laboratory data: abnormal liver function tests (increased serum alkaline phosphatase,
28
29 248 gamma-glutamyltransferase (gamma-GT), aspartate transaminase (AST) and ALT
30
31 249 levels (defined as more than 1.5 times the ULN))

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33
34 250 3. Imaging

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37 251 a. Biliary dilatation

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40 252 b. Evidence of the etiology on imaging (stricture, stone, stent etc.) (26)

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46 254 Obstructive choledocholithiasis: presence of gallstones, microlithiasis or biliary sludge in the CBD on
47
48 255 imaging, requiring an ERCP, according to the treating physician.

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284 [I&HD=180221-1109&HDR=G1&STB=T](http://statline.cbs.nl/Statweb/publication/?VW=T&DM=SLNL&PA=37312&D1=a&D2=0,5,10,(1-2)-&HD=180221-1109&HDR=G1&STB=T).

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Additional file 3: Short Form 36 Questionnaire

English version

1. In general, would you say your health is:
- excellent
 - very good
 - good
 - fair
 - poor
2. **Compared to one year ago**, how would you rate your health in general **now**?
- much better now than one year ago
 - somewhat better now than one year ago
 - about the same
 - somewhat worse now than one year ago
 - much worse now than one year ago

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3. The following items are about activities you might do during a typical day.
Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Lifting or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Climbing several flights of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Climbing one flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Bending, kneeling, or stooping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Walking more than a mile	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Walking several blocks	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Walking one block	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Bathing or dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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4 4. During the **past 4 weeks**, have you had any of the following problems with
5 your work or other regular daily activities **as a result of your physical**
6 **health**?

- | | Yes | No |
|---|--------------------------|--------------------------|
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| 11 | | |
| 12 a. Cut down the amount of time you | <input type="checkbox"/> | <input type="checkbox"/> |
| 13 spent on work or other activities | | |
| 14 | | |
| 15 b. Accomplished less than you | <input type="checkbox"/> | <input type="checkbox"/> |
| 16 would like | | |
| 17 | | |
| 18 | | |
| 19 c. Were limited in the kind of work | <input type="checkbox"/> | <input type="checkbox"/> |
| 20 or other activities | | |
| 21 | | |
| 22 | | |
| 23 d. Had difficulty performing the | <input type="checkbox"/> | <input type="checkbox"/> |
| 24 work or other activities (for | | |
| 25 example, it took extra effort) | | |
| 26 | | |
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32 5. During the **past 4 weeks**, have you had any of the following problems with
33 your work or other regular daily activities **as a result of any emotional**
34 **problems** (such as feeling depressed or anxious)?

- | | Yes | No |
|--|--------------------------|--------------------------|
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| 40 a. Cut down the amount of time you | <input type="checkbox"/> | <input type="checkbox"/> |
| 41 spent on work or other activities | | |
| 42 | | |
| 43 | | |
| 44 b. Accomplished less than you | <input type="checkbox"/> | <input type="checkbox"/> |
| 45 would like | | |
| 46 | | |
| 47 | | |
| 48 c. Didn't do work or other activities | <input type="checkbox"/> | <input type="checkbox"/> |
| 49 as carefully as usual | | |
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6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
- not at all
 slightly
 moderately
 quite a bit
 extremely

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7. How much **bodily** pain have you had during the **past 4 weeks**?
- none
 very mild
 mild
 moderate
 severe
 very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?
- not at all
 a little bit
 moderately
 quite a bit
 extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks ...	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Have you been a very nervous person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Have you felt calm and peaceful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Did you have a lot of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Have you felt downhearted and blue?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Did you feel worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Have you been a happy person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Did you feel tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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10. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?
- all of the time
 most of the time
 some of the time
 a little of the time
 none of the time

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11. How TRUE or FALSE is **each** of the following statements for you?

- | | Definitely true | Mostly true | Don't know | Mostly false | Definitely false |
|--|--------------------------|--------------------------|-------------------------------------|--------------------------|--------------------------|
| a. I seem to get sick a little easier than other people. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. I am as healthy as anybody I know. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. I expect my health to get worse. | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. My health is excellent. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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Space for additional remarks with the questionnaire:

Dutch version

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1. Wat vindt u, over het algemeen genomen, van uw gezondheid?
- uitstekend
 - zeer goed
 - goed
 - matig
 - slecht
2. In vergelijking met 1 jaar geleden, hoe zou u nu uw gezondheid in het algemeen beoordelen?
- veel beter dan een jaar geleden
 - iets beter dan een jaar geleden
 - ongeveer hetzelfde als een jaar geleden
 - iets slechter dan een jaar geleden
 - veel slechter dan een jaar geleden

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3. De volgende vragen gaan over dagelijkse bezigheden. Wordt u door uw **gezondheid op dit moment** beperkt bij deze bezigheden? Zo ja, in welke mate?

	Ja, ernstig	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. <i>Forse inspanning</i> (zoals hardlopen, zware voorwerpen tillen, inspannend sporten)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. <i>Matige inspanning</i> (zoals het verplaatsen van een tafel, stofzuigen, fietsen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Tillen of boodschappen dragen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. <i>Een paar</i> trappen oplopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. <i>Eén</i> trap oplopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Buigen, knielen of bukken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. <i>Meer dan een kilometer</i> lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Een halve kilometer lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. <i>Honderd meter</i> lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Uzelf wassen of aankleden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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4 4. Had u, ten gevolge van uw **lichamelijke gezondheid**, *de afgelopen 4 weken*
5 één van de volgende problemen bij uw werk of andere bezigheden?
6

7
8 **Ja**

Nee

9
10 a. U heeft *minder tijd* kunnen
11 besteden aan werk of andere
12 bezigheden.

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15 b. U heeft *minder bereikt* dan u zou
16 willen.

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19 c. U was beperkt in het *soort* werk
20 of soort bezigheden.

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23 d. U had moeite met het werk of
24 andere bezigheden (het kostte u
25 bijvoorbeeld extra inspanning).
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32 5. Had u, ten gevolge van een **emotioneel probleem** (bijvoorbeeld doordat u
33 zich depressief of angstig voelde), *de afgelopen 4 weken* één van de
34 volgende problemen bij uw werk of andere bezigheden?
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38 **Ja**

Nee

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40 a. U heeft *minder tijd* kunnen
41 besteden aan werk of andere
42 bezigheden.

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45 b. U heeft *minder bereikt* dan u zou
46 willen.

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49 c. U heeft het werk of andere
50 bezigheden niet zo zorgvuldig
51 gedaan als u gewend bent.
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6. In hoeverre heeft uw **lichamelijke gezondheid** of hebben uw **emotionele problemen** u *de afgelopen 4 weken* belemmerd in uw normale sociale bezigheden met gezin, vrienden, buren of anderen?
- helemaal niet
 enigszins
 nogal
 veel
 heel erg veel
7. Hoeveel **pijn** had u *de afgelopen 4 weken*?
- geen
 heel licht
 licht
 nogal
 ernstig
 heel ernstig
8. In welke mate heeft **pijn** u *de afgelopen 4 weken* belemmerd bij uw normale werkzaamheden (zowel werk buitenshuis als huishoudelijk werk)?
- helemaal niet
 enigszins
 nogal
 veel
 heel erg veel

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12. De volgende vragen gaan over hoe u zich *de afgelopen 4 weken* heeft **gevoeld**. Wilt u bij elke vraag het antwoord aankruisen dat het beste aansluit bij hoe u zich heeft gevoeld?

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Hoe vaak
gedurende *de*
afgelopen 4
weken:

Voortdurend **Meestal** **Vaak** **Soms** **Zelden** **Nooit**

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|----|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a. | voelde u zich levenslustig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. | voelde u zich erg zenuwachtig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. | zat u zo erg in de put dat niets u kon opvrolijken? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. | voelde u zich kalm en rustig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e. | voelde u zich erg energiek? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f. | voelde u zich neerslachtig en somber? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g. | voelde u zich uitgeblust? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h. | voelde u zich gelukkig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i. | voelde u zich moe? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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10. *Hoe vaak* hebben uw **lichamelijke gezondheid of emotionele problemen** gedurende *de afgelopen 4 weken* uw sociale activiteiten (zoals bezoek aan vrienden of naaste familieleden) belemmerd?
- voortdurend
 meestal
 soms
 zelden
 nooit

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11. Wilt u het antwoord kiezen dat het beste weergeeft hoe juist of onjuist u elk van de volgende uitspraken voor uzelf vindt?

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	Volkomen juist	Grotendeels juist	Weet ik niet	Grotendeels onjuist	Volkomen onjuist
a. Ik lijk gemakkelijker ziek te worden dan andere mensen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Ik ben net zo gezond als andere mensen die ik ken.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Ik verwacht dat mijn gezondheid achteruit zal gaan.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Mijn gezondheid is uitstekend.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Ruimte voor aanvullende opmerkingen bij de vragenlijst:

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The role of endoscopic ultrasonography in the diagnostic work-up of idiopathic acute pancreatitis (PICUS): study protocol for a nationwide prospective cohort study

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7 2 idiopathic acute pancreatitis (PICUS): study protocol for a nationwide
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11 3 prospective cohort study
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53 66 **List of abbreviations**

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56 67 ALT = alanine aminotransferase

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59 68 BMI = body mass index

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3 69 CI = confidence interval
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6 70 CRF = case report form
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9 71 CT = computed tomography
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12 72 ERCP = endoscopic retrograde cholangiopancreatography
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15 73 EUS = endoscopic ultrasonography
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18 74 GRADE = Grading of Recommendations Assessment, Development and Evaluation
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21 75 IAP = idiopathic acute pancreatitis
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24 76 IAP/APA = International Association of Pancreatology/American Pancreatic Association
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27 77 IPMN = intraductal papillary mucinous neoplasm
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30 78 IQR = interquartile range
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33 79 MRCP = magnetic resonance cholangiopancreatography
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36 80 MRI = magnetic resonance imaging
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3 88 Abstract

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6 89 Introduction

7
8 90 Idiopathic acute pancreatitis (IAP) remains a dilemma for physicians as it is uncertain whether patients
9
10 91 with IAP may actually have an occult etiology. It is unclear to what extent additional diagnostic
11
12 92 modalities such as endoscopic ultrasonography (EUS) are warranted after a first episode of IAP in order
13
14 93 to uncover this etiology. Failure to timely determine treatable etiologies delays appropriate treatment
15
16 94 and might subsequently cause recurrence of acute pancreatitis. Therefore, the aim of the “Pancreatitis
17
18 95 of Idiopathic origin: Clinical added value of endoscopic UltraSonography” (PICUS) study is to determine
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20 96 the value of routine EUS in determining the etiology of pancreatitis in patients with a first episode of
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22 97 IAP.
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30 99 Methods and analysis

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32 100 PICUS is designed as a multicenter prospective cohort study of 106 patients with a first episode of IAP
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34 101 after complete standard diagnostic work-up, in whom a diagnostic EUS will be performed. Standard
35
36 102 diagnostic work-up will include a complete personal and family history, laboratory tests including
37
38 103 serum alanine aminotransferase, calcium and triglyceride levels, and imaging by transabdominal
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40 104 ultrasound, magnetic resonance imaging or magnetic resonance cholangiopancreatography after
41
42 105 clinical recovery from the acute pancreatitis episode. The primary outcome measure is detection of
43
44 106 etiology by EUS. Secondary outcome measures include pancreatitis recurrence rate, severity of
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46 107 recurrent pancreatitis, readmission, additional interventions, complications, length of hospital stay,
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48 108 quality of life, mortality and costs, during a follow-up period of 12 months.
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3 110 Ethics and dissemination
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5 111 PICUS is conducted according to the Declaration of Helsinki and Guideline for Good Clinical Practice.
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8 112 Five Medical Ethics Review Committees assessed PICUS (Medical Ethics Review Committee of
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10 113 Academic Medical Center, University Medical Center Utrecht, Radboud university medical center,
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12 114 Erasmus Medical Center and Maastricht University Medical Center). The results will be submitted for
13

14 115 publication in an international peer-reviewed journal.
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20 117 Trial registration
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23 118 Netherlands Trial Register: NL7066, June 9th 2018. Prospectively registered.
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32 121 Article summary: strengths and limitations
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34 122 • This is the first prospective cohort study of only patients with a single episode of presumed
35 123 IAP.

36 124 • This is the first prospective cohort study which only includes patients after complete
37 125 standard diagnostic work-up (including exclusion based on blood serum ALT and imaging
38 126 after clinical recovery).

39 127 • The multicenter nature of this study reduces the risk of patient selection bias.
40
41

42 128 • This study has a follow-up time of a year, and thus this study could elucidate the previously
43 129 hypothesized association between EUS, detection of etiology and subsequent treatment of
44 130 etiology, and pancreatitis recurrence.

45 131 • As the timing of the EUS is set to be after clinical recovery from pancreatitis in this trial, no
46 132 conclusions on the diagnostic yield of EUS in a different time frame can be drawn from this
47 133 study.
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135 Keywords

136 Idiopathic acute pancreatitis; endoscopic ultrasonography, etiology

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139 Background

140 Acute pancreatitis can be induced by numerous causes. Gallstone disease (approximately 50%) and
141 alcohol (approximately 20%) are the most frequent causes (1-6), although the prevalence of etiologies
142 of acute pancreatitis is dependent on, among other things, age and geographical factors (7-10). There
143 is, however, a considerable group of patients of approximately 25% in whom no etiology can be found
144 after routine diagnostic work-up (i.e. medical history, laboratory investigations and transabdominal
145 ultrasound). These patients are considered to have presumed idiopathic acute pancreatitis (IAP) (3).

146 When IAP is presumed, guidelines recommend repeat transabdominal ultrasound after
147 discharge (11, 12). This repeat ultrasonography has an additional diagnostic yield of 20% for the
148 detection of gallstones or sludge in these patients (13). Undetected microlithiasis and biliary sludge
149 are generally considered to be the major cause of presumed IAP (14, 15). Undetected and subsequently
150 untreated gallstone disease poses a risk for recurrent acute pancreatitis and other biliary events, e.g.
151 cholecystitis, biliary colic's and cholangitis.

152 Therefore, when previous diagnostics failed to uncover an etiology, endoscopic
153 ultrasonography (EUS) should be considered for the detection of biliary disease or other abnormalities
154 causing pancreatitis, such as neoplasms and chronic pancreatitis (11, 12, 16, 17). EUS is advised as the
155 first step in presumed IAP, followed by (secretin-enhanced) magnetic resonance
156 cholangiopancreaticography (MRCP) to identify rare morphologic abnormalities (11), as EUS is
157 considered to have a higher diagnostic yield than MRCP for clinically relevant causes (18).

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3 158 Although guidelines do recommend performing EUS after a first or second attack of presumed
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5 159 IAP, this recommendation is scored as a mere grade 2C, according to the Grading of Recommendations
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7 160 Assessment, Development and Evaluation (GRADE) classification (19) (indicating a weak
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10 161 recommendation based on evidence of low quality, with weak agreement among experts in this field)
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12 162 (11). Therefore, EUS is not routinely performed as the exact significance in this patient group is unclear
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14 163 (11, 16).

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17 164 The PICUS study was designed to determine whether routine EUS should be incorporated in
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19 165 the standard diagnostic work-up of a first episode of presumed IAP.
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28 168 Methods and analysis

29 30 31 169 Study aim

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33 170 The objective of this study is to determine the diagnostic yield of EUS for the detection of etiology in
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35 171 patients with a first episode of presumed IAP.
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39 172 Depending on the diagnostic yield of EUS observed in the PICUS study, incorporation of EUS
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41 173 in routine diagnostic work-up of patients with a first episode of presumed IAP will be considered. A
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43 174 minimal diagnostic yield of 10% for any etiology will be regarded as reasonable to justify implementing
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45 175 routine EUS in the standard diagnostic work-up of a first episode of presumed IAP.
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52 177 Study design and setting

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54 178 PICUS is a multicenter prospective cohort study. A total of 106 patients will be included from 28
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56 179 participating Dutch centers, including all 8 university centers and 20 large teaching hospitals. A listing
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3 180 of the participating centers is included in the Authors' information. An overview of the study design,
4
5 181 including screening procedures and follow-up, is provided in figure 1.
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11 183 Study population

13 184 The subjects of this study have had a first episode of acute pancreatitis, as defined by the 2012 Revised
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16 185 Atlanta criteria (20), with an unknown origin after standard diagnostic work-up, according to the 2013
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18 186 International Association of Pancreatology/American Pancreatic Association (IAP/APA) evidence-
19
20 187 based guidelines on management of acute pancreatitis (11). The diagnostic modalities that constitute
21
22 188 standard diagnostic work-up are listed in table 1 and additional file 1. The diagnostic tests as laid out
23
24 189 in table 1 are to be performed in all subjects and these tests cannot show any signs of an etiology in
25
26 190 all subjects. Potential etiologies and their definitions are listed in table 2 and additional file 1.
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30 191

32 192 Eligibility criteria

34 193 The inclusion criteria are:

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38 194 1. Patients of 18 years or older
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40 195 2. First episode of presumed IAP after standard diagnostic work-up, as defined by the IAP/APA
41
42 196 evidence-based guidelines on management of acute pancreatitis (11)
43
44 197 3. Informed consent for participation
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46

47 198

49 199 The exclusion criteria are:

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53 200 1. Known etiology
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55 201 2. Chronic pancreatitis, as defined by the M-ANNHEIM criteria (21)
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57 202 3. Recurrent pancreatitis
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3 203 4. Altered anatomy which prohibits the endosonographer from visualizing the gall bladder, bile
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5 204 ducts, pancreas or pancreatic duct via EUS (e.g. gastric bypass surgery)
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7 205 5. Diagnostic EUS aimed to determine etiology before inclusion
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12
13 207 Endoscopic ultrasonography

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15 208 EUS will be performed in routine clinical practice by an endosonographer. Use of linear or radial EUS
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17 209 will be at the discretion of the endosonographer. All Dutch endosonographers are trained to perform
18
19 210 EUS according to the technique of Hawes and Fockens (22).
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23 211 The endosonographer will systematically report, using a standardized Case Report Form (CRF),
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25 212 the experience of the endosonographer, visualization of anatomical structures (i.e. gall bladder,
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27 213 common bile duct and pancreatic duct), presence of local complications of acute pancreatitis,
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29 214 characteristics of biliary etiology (i.e. gallstones, microlithiasis and/or biliary sludge), characteristics of
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31 215 chronic pancreatitis, presence of (a) pancreatic or peri-ampullary benign or malignant tumor(s),
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33 216 characteristics of auto-immune pancreatitis, anatomic variations (e.g. pancreas divisum) or other
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35 217 anomalies (e.g. cholecystitis, vascular, renal, splenic or hepatic anomalies or ascites), and performance
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37 218 of fine needle aspiration or fine needle biopsy. Additionally, the type of endoscope, use of sedation,
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39 219 procedure related complications and results of the fine needle aspiration or biopsy will be
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41 220 systematically recorded by the study coordinator in a separate CRF.
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49 222 Primary outcome measure

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51 223 The primary outcome measure is the number and ratio of patients with presumed IAP in whom EUS
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53 224 detects a cause for the pancreatitis episode.
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56 225 A positive EUS is defined as an EUS during which a definitive cause for the acute pancreatitis
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58 226 episode has been found; or during which abnormalities are visualized constituting a definitive cause,
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227 after obtaining tissue and pathological examination. An overview of the exact findings scored as
228 positive imaging is provided in table 3.

229 If during EUS pancreatic abnormalities are found, yet not enough to make a certain diagnosis
230 of chronic pancreatitis according to the M-ANNHEIM classification (21), this imaging is considered to
231 be negative, even though it did show abnormalities. This approach is chosen because the aim of this
232 study is to determine the rate of which EUS can find a cause for the presumed IAP episode. For the
233 same reason, report of an anatomical abnormality during EUS after a first episode of acute pancreatitis
234 is not scored as positive imaging as pancreatic morphological changes are very common in IAP and not
235 necessarily clinically relevant, as is elaborated on in the discussion (23).

236

237 Secondary outcome measures

238 The secondary outcome measures are recurrence rate of acute pancreatitis, severity of recurrent
239 pancreatitis (20), readmission, performance of additional invasive procedures (e.g. cholecystectomy,
240 endoscopic sphincterotomy), complications of EUS and of additional interventions, according to the
241 Clavien-Dindo classification (24), length of hospital stay, quality of life, mortality and costs. Relevant
242 definitions are reported in Additional File 2.

243

244 Sample size calculation

245 The sample size calculation was based on the primary outcome measure, diagnostic yield of EUS. Based
246 on two previous studies reporting yield in patients with a first episode of presumed IAP (25, 26),
247 adjusted for the PICUS study criteria for inclusion (i.e. requiring negative imaging after clinical
248 recovery) and for positive imaging (i.e. excluding pancreas divisum as etiology), diagnostic yield was
249 assumed to be 30%. Using a two-sided significance level (α) of 0.05, a power ($1 - \beta$) of 80%, 95 patients
250 are needed to attain a 95% confidence interval (CI) with a range smaller than 10% above and below

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3 251 the assumed yield of 30% (95% CI: 20.8, 39.2). Assuming a drop-out rate of 10%, a total of 106 patients
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5 252 will be included (27). The sample size was calculated using the software programs RStudio (28) and
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7 253 nQuery (29).
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12 13 255 Follow-up

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16 256 Data from patient records on primary and secondary outcome measures will be collected until 1 year
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18 257 after inclusion. Outpatient care and follow-up after the EUS is at the discretion of the treating
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20 258 physician, but an outpatient clinic visit after EUS to discuss the results of the EUS and potential
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22 259 subsequent appropriate treatment can be considered standard care.
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26 260 In case of biliary disease, the patient will be considered for endoscopic retrograde
27
28 261 cholangiopancreatography (ERCP) with sphincterotomy when choledocho(-micro-)lithiasis or sludge
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30 262 in the common bile duct is present, and cholecystectomy, as is standard care for biliary pancreatitis. A
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32 263 (secretin-enhanced) MRCP will be recommended, if not performed earlier, if a patient is readmitted
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34 264 for a recurrent episode of acute pancreatitis after a negative EUS for etiology, in order to rule out
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36 265 structural anomalies such as pancreas divisum. This is in accordance with current guidelines (11).
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40 266 Patients will be asked to fill out the Short Form-36 questionnaire in the validated Dutch
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42 267 translation on day 3 after inclusion, after 6 months and after 1 year. This questionnaire in both English
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44 268 and Dutch is included in additional file 3.
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48 49 50 270 Statistical aspects

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52 271 All included subjects will be evaluated for primary and secondary endpoints until 1 year after inclusion.
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54 272 The primary analysis will be based on intention-to-treat principles. For exploratory reasons a per-
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56 273 protocol analysis will be performed too.
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3 274 The intention-to-treat population comprises all patients included in the study, regardless of
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5 275 adherence to study protocol. The per-protocol population is the subset of included patients who were
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7 276 treated with the guidelines of the protocol (i.e. meeting all eligibility criteria including all of the
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10 277 diagnostic tests required for the diagnosis of IAP, undergoing EUS as described in the “Endoscopic
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12 278 ultrasonography section”). A tabular listing of all patients excluded from the intention-to-treat
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14 279 population will be provided together with the reasons for exclusion.

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17 280 All analyses will be performed in SPSS for Microsoft Windows. All data handling and analysis
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19 281 will be saved in a syntax-file. Results will be presented with all centers combined. A two-tailed p-value
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22 282 of < 0.05 is considered statistically significant.

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28 284 ***Baseline variables***

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30 285 The reported baseline characteristics consist of age, sex, body mass index (BMI), previous
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32 286 cholecystectomy, nicotine and alcohol use, severity of pancreatitis, length of hospital stay, amylase,
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34 287 lipase, C-reactive protein, alanine transaminase, calcium, albumin and triglycerides levels in blood
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37 288 serum on admission, imaging modalities before EUS and their findings. Baseline characteristics of EUS
38
39 289 will include timing of EUS, experience of endosonographer and type of sedation and type of endoscope
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41 290 used. Data will be presented in percentages or as mean with standard deviation, or in case of a skewed
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43 291 distribution as median with interquartile range (IQR).

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50 293 ***Primary outcome measure: etiology detection rate***

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52 294 Overall detection rate of an etiology for the episode of acute pancreatitis will be presented as
53
54 295 percentage with a 95% CI. Predefined subgroup analyses will be made for patients with and without
55
56 296 obesity (cut-off at a BMI of 30), a previous cholecystectomy, alcohol use and local complications from
57
58
59 297 the IAP episode. A subgroup analysis will also be made for patients with a transabdominal ultrasound
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3 298 as imaging after clinical recovery and with magnetic resonance imaging (MRI) or MRCP as imaging after
4
5 299 clinical recovery. Finally, a subgroup analysis will be made for EUS performed by endosonographers
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7 300 with and without extensive experience (cut-off at 400 endosonographies performed), use of linear or
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9
10 301 radial scope and type of sedation used. In subgroup analyses, the Chi-square test or the Fisher's exact
11
12 302 test will be used, as appropriate, to compare etiology detection rate between subgroups. In subgroup
13
14 303 analyses, comparability between groups regarding baseline variables will be checked. If the subgroups
15
16 304 differ statistically significantly in one or more baseline variables, this will be corrected in a logistic
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19 305 regression analysis.
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25 307 ***Secondary outcome measures***

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27 308 Secondary outcome measures will be described as percentages with 95% CI, as mean with standard
28
29 309 deviation or median with IQR, as appropriate.
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33 310 For recurrence rate, subgroup analyses will be made for patients with a positive and negative
34
35 311 EUS, and in patients with a positive EUS, for patients who were and were not treated adequately. The
36
37 312 same subgroup analyses as in the primary outcome measure, will also be applied on the recurrence
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39 313 rate. The Chi-square test or the Fisher's exact test will be used for comparison between subgroups, as
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41 314 appropriate.
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45 315 For quality of life, subgroup analyses will be made for baseline versus follow-up quality of life
46
47 316 and for patients with a positive and negative EUS, and with and without pancreatitis recurrence during
48
49 317 follow-up. The (un-)paired T-test, Wilcoxon signed rank test or the Mann-Whitney U test will be used
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51 318 for comparisons between subgroups, as appropriate.
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320 **Cost analysis**

321 The cost analysis will comprise direct medical costs, which are generated by healthcare utilization and
322 include hospital admission periods and therapeutic and diagnostic procedures (30). Estimates of unit
323 costs will be based on Dutch reference data from the cost guide of the Dutch Health Council (31). If
324 this guide is an inappropriate determination of unit costs, the costs will be based on data provided by
325 two hospital administrations (one university center and one general hospital) to account for the actual
326 input of personnel, material and overhead over hospital resources used. Cost calculations will be used
327 to determine cost of interventions (surgical, endoscopic or radiological) and diagnostic imaging. The
328 cost analysis will be reported separately from the main study manuscript.

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330 Patient and public involvement

331 The patient advocacy organization '*Alveeskliervereniging Nederland*' was involved in the design of the
332 PICUS study. The experience of the patient advocacy organization with IAP and participation in
333 scientific research has driven the research question and design of the study with regards to patient
334 burden. The patient advocacy organization will also be involved in the dissemination and
335 implementation of the study results.

336 All patients eligible for participation will be asked to give written informed consent.

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339 Ethics and dissemination

340 The PICUS study is conducted according to the principles of the Declaration of Helsinki (October 2013)
341 and to the Guideline for Good Clinical Practice by the International Council for Harmonization
342 (November 9 2016).

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3 343 The need for ethical approval was waived by the Medical Ethics Review Committee of the
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5 344 Academic Medical Center on May 28, 2018 (W18_161 # 18.199), by the Medical Research Ethics
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7 345 Committee of the University Medical Center Utrecht on July 04, 2018 (18-469), by the Research Ethics
8
9 346 Committee of Radboud university medical center on July 23, 2018 (2018-4520), by the Medical Ethics
10
11 347 Review Committee of the Erasmus Medical Center on July 30, 2018 (MEC-2018-1293) and by the
12
13 348 Medical Ethics Review Committee of the Maastricht University Medical Center on September 7, 2018
14
15 349 (2018-0685). Before start of inclusion, local board approval will be obtained in all participating centers.
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19 350 The results of the PICUS study will be submitted for publication in an international peer-
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21 351 reviewed scientific journal, regardless of study outcomes.
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30 354 Discussion

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33 355 Previous research has suggested that EUS might be beneficial in the detection of an etiology in
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35 356 presumed IAP. However, data lacks on the efficacy of routine EUS in patients with a first episode of
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37 357 presumed IAP, after repeat imaging after clinical recovery is negative for an etiology. The PICUS study
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39 358 aims to determine whether routine EUS is warranted in a first episode of acute pancreatitis where no
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41 359 cause could be uncovered after complete standard diagnostic work-up.
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45 360 Currently, guidelines do not clearly define criteria for biliary origin (11). However, it is generally
46
47 361 agreed upon that cholelithiasis, microlithiasis or biliary sludge constitute biliary etiology. Several
48
49 362 previous studies have shown an association between elevated ALT levels and acute biliary pancreatitis
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51 363 (32-35), with a positive predictive value of 85% for an ALT > 150 U/L within 48 hours after onset of
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53 364 symptoms (11, 32, 33, 35). Therefore, an elevated blood serum ALT level at admission is considered to
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55 365 entail a high probability of biliary etiology, and pancreatitis with an elevated ALT is treated as being of
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57 366 biliary origin (32-34, 36). However, the majority of current literature on EUS did not exclude patients
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3 367 based on ALT level at admission (15, 25, 26, 32, 37-46). As these patients have a higher a priori chance
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5 368 of confirmation of biliary etiology on EUS, the etiology detection rate of EUS might be overestimated
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7 369 in these studies. In PICUS, biliary etiology is defined as either the signs of cholelithiasis, microlithiasis
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10 370 or biliary sludge on transabdominal ultrasonography, or transient elevation of the blood serum ALT
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12 371 level of more than twice the upper limit of normal at admission in the absence of ALT elevating
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14 372 comorbidity. By only including patients with normal or slightly elevated ALT levels at admission, the
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16 373 etiology detection rate as reported in PICUS will reflect the detection rate in patients who are truly
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18 374 considered as having presumed IAP after standard diagnostic work-up.

21 375 Multiple definitions for IAP are maintained in literature (47). For PICUS, the definition provided
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23 376 by the IAP/APA evidence-based guidelines on management of acute pancreatitis was used (11). These
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25 377 guidelines advise a repeat transabdominal ultrasound after clinical recovery in the work-up of
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27 378 presumed IAP because the index transabdominal ultrasound is less sensitive during the acute phase of
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29 379 pancreatitis. The subpar visualization of gall bladder, bile ducts and pancreas is often due to excessive
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31 380 amounts of air in the intestines caused by pancreatitis-induced ileus and/or suboptimal cooperation
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33 381 of painful patients (48). After the first episode of acute pancreatitis, repeating a transabdominal
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35 382 ultrasound may be able to detect biliary stones where it could not during index admission (49). Of the
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37 383 current literature on EUS in IAP, however, only a minority of studies included repeat imaging in the
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39 384 diagnostic work-up before EUS (15, 40, 41, 43). Previous research has shown that a repeat
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41 385 transabdominal ultrasound has a diagnostic yield of 20% in patients with a first episode of IAP (13).
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43 386 Omitting repeat imaging from diagnostic work-up before EUS may lead to an overestimation of the
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45 387 diagnostic yield of EUS. In PICUS, all patients are required to undergo imaging after clinical recovery,
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47 388 i.e. transabdominal ultrasound or MRI/MRCP. Computed tomography (CT) is not considered sufficient
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49 389 imaging as biliary disease, the most common underlying etiology in presumed IAP, cannot always be
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51 390 adequately detected using CT.
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3 391 It is well documented that the overall diagnostic yield of EUS in patients with recurrent
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5 392 pancreatitis is superior to the diagnostic yield of both secretin-enhanced MRCP (s-MRCP) and non-
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7 393 secretin-enhanced MRCP (18, 44, 46, 50). In the subgroup of patients with a pancreas divisum,
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9 394 however, s-MRCP is considered to be superior in diagnostic yield to both EUS and MRCP (18). The role
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11 395 of pancreas divisum in the etiology of pancreatitis is unclear. Epidemiological studies have shown that
12
13 396 the prevalence of pancreas divisum in the general population is equal to the prevalence in patients
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15 397 with presumed IAP (23). In patients with a pancreas divisum and acute pancreatitis, potentially other
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17 398 disease modifying factors add to the occurrence of pancreatitis, such as increased sensitivity to toxins
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19 399 or genetic susceptibility. Because of this ambiguity, pancreas divisum in patients with a first episode
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21 400 of acute pancreatitis is mostly left untreated in clinical practice. However, if patients with a pancreas
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23 401 divisum present with multiple episodes of presumed IAP, the divisum is often considered to be related
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25 402 to the pancreatitis and is subsequently treated, often with ERCP with endoscopic sphincterotomy,
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27 403 although evidence supporting this practice is limited (23). Because of both the diagnostic superiority
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29 404 of EUS in recurrent pancreatitis as well as the lack of clinical consequences of (s-)MRCP in patients with
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31 405 a first episode of pancreatitis, EUS is preferred to (s-)MRCP as the first choice for additional diagnostic
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33 406 testing for etiology in patients with presumed IAP (18, 44, 46, 50). Subsequently, current guidelines
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35 407 advise performing MRCP in case of recurrent IAP after EUS fails to determine an etiology (11).
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37 408 Therefore, in PICUS, we have chosen not to systematically include (s-)MRCP in the diagnostic work-up
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39 409 before EUS of first episode IAP.

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46 410 Current guidelines advise consideration of EUS after a first or second attack of IAP (11).
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48 411 However, there is a paucity of evidence on the efficacy of EUS in first episode IAP. Three previous
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50 412 studies prospectively reported on EUS in patients with first episode IAP (25, 26, 38). However, in these
51
52 413 studies, patients were not excluded based on liver enzymes abnormalities suggestive of biliary disease
53
54 414 and no repeat imaging after clinical recovery was performed. PICUS will be the first prospective cohort
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56 415 study in which EUS will be performed in patients with a first episode of IAP after complete standard
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58 416 diagnostic work-up before EUS according to current guidelines (11).
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3 417 A diagnostic yield of 10% for any etiology will be considered reasonable to justify incorporating
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5 418 routine EUS after a first episode of presumed IAP. This cut-off value was determined during a
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7 419 multidisciplinary meeting of the Dutch Pancreatitis Study Group, which included the principal
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9 420 investigators of several trials being executed by the Dutch Pancreatitis Study Group. Considering the
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11 421 expectation that the majority of uncovered etiologies by EUS will be treatable (e.g. biliary disease) and
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13 422 adequate treatment could prevent pancreatitis recurrence, while in a minority of uncovered etiologies
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15 423 diagnosis before progression of disease might be crucial for prognosis (e.g. malignancy), a positive
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17 424 result in 10% of patients was deemed sufficient to warrant routine EUS after a first episode of
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19 425 presumed IAP.
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24 426 In conclusion, the PICUS study is the first prospective cohort study of patients with a single
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26 427 episode of presumed IAP after complete standard diagnostic work-up (including exclusion based on
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28 428 blood serum ALT and imaging after clinical recovery). The results of the PICUS study will establish
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30 429 whether routine EUS should be incorporated in the guidelines for standard diagnostic work-up after a
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32 430 first episode of presumed IAP.
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54
55 439 study, and
56
57
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- 1
2
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4
5 441 their effort in representing the perspective of (participating) patients during the study design.
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11 443 **References**
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28 606 Author Statement
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30 607 Authors' contributions
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33 608 DSU drafted the manuscript. HCT, RCV, SAB, MGB and JEvH co-authored the writing of the manuscript.
34
35 609 DSU, RCV, SAB, MABo, MJB, PF, EJMvG, JWP, HCvS, FPV, MGB and JEvH were involved in the design of
36
37 610 the study during several meetings of the Dutch Pancreatitis Study Group. NDHL, MPGFA, AB, RAB,
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39 611 MABr, LH, WLC, HMvD, BCvE, GWE, WLH, CVH, AI, LMK, SDK, LEP, RQ, TEHR, ACITLT, AYT, NGV, AMCJV,
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41 612 RLJvW and BJW critically assessed the study design, during several meetings, and edited the
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43 613 manuscript. All authors read and approved the final manuscript.
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53
54 617 number D17-25). The PICUS study is an investigator-initiated study. The sponsor had no influence on
55
56 618 design, implementation and conduct of the study, as well as on collection, analysis and interpretation
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58 619 of data, construction of the manuscript and decision to publish.
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6 621 Competing interests statement

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8 622 The authors declare that they have no competing interests.
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14 624 Data Availability Statement

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17 625 The datasets used and/or analyzed during the current study are available from the corresponding
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19 626 author on reasonable request.
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28 629 Figure legend

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30 630 Figure 1: Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP =
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32 631 magnetic resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic
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34 632 ultrasonography.
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640 Table 1

Standard diagnostic work-up	
<i>Detailed personal and family history, including questions on:</i>	Alcohol use
	Recent ERCP
	Recent start or changes in use of drugs associated with acute pancreatitis
	Recent major abdominal trauma
	Recent abdominal surgery
	Familial and hereditary pancreatitis
	Cystic fibrosis-related pancreatitis
<i>Laboratory tests, including:</i>	Blood serum triglycerides level
	Blood serum calcium level, corrected for the blood serum albumin level
	Blood serum ALT level on admission
<i>Imaging:</i>	Transabdominal ultrasound, MRI or MRCP after clinical recovery

641 **Table 1: Standard diagnostic work-up** Standard diagnostic work-up according to the 2013 IAP/APA evidence-based guideline
 642 on management of acute pancreatitis. A listing of the drugs considered to be associated with acute pancreatitis are listed in
 643 additional file 1. ERCP = endoscopic retrograde cholangiopancreatography; ALT = alanine aminotransferase; MRI = magnetic
 644 resonance imaging; MRCP = magnetic resonance cholangiopancreatography.

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651 Table 2

Etiology	Definition
Alcohol	> 4 units of alcohol in the 24 hours prior to start of abdominal complaints (51-53)
Biliary disease	<ol style="list-style-type: none"> 1. A transient elevated ALT level of >2 times the upper limit of normal at diagnosis of acute pancreatitis, in the absence of other ALT elevating comorbidity (34), OR 2. Gallstones, microlithiasis and/or biliary sludge, OR 3. A dilated CBD of >8 mm in patients <76 years or >10 mm in patients >75 years at diagnosis of acute pancreatitis (36)
Cystic fibrosis	history of cystic fibrosis in the absence of another origin (54)
Familial	two or more direct blood-related family members (parents, children or siblings) who have had an episode of acute pancreatitis (55-57)
Hereditary	mutation in the PRSS1, SPINK1, CFTR, CTSC, CLDN2 or CPA1 gene, or direct family member (parents, children, siblings) with one or more of the above mentioned mutations and at least one direct family member who has (had) acute or chronic pancreatitis (57, 58)
Hypercalcemia	blood serum calcium level ≥ 12 mg/dl (3 mmol/l), corrected for serum albumin level, as first measured during admission (59)
Hypertriglyceridemia	blood serum triglyceride level of ≥ 1000 mg/dl (11.2 mmol/l) under fasting conditions, as first measured during admission (60)
Medication	use of drug(s) listed in additional file 1, which has or have been started or increased in dosage within a reasonable temporal sequence, in principle 1

	month before onset of pancreatitis, and has or have a positive dechallenge (a drug reaction that is confirmed by stopping the drug) (61, 62)
Neoplasm	Known hepatopancreatobiliary malignancy or known malignancy with metastases causing obstruction of the pancreatic duct (63)
ERCP	ERCP within 24 hours before diagnosis of pancreatitis (64)
Surgical	abdominal surgery within 24 hours prior to diagnosis of pancreatitis (65)
Trauma	typical blunt trauma to the upper abdomen and pancreatic trauma visible on imaging (66)

652 **Table 2: potential etiologies and their definitions** Potential etiologies and their definitions. Side branch or mixed type
653 *intraductal papillary mucinous neoplasms without dilatation of the pancreatic duct and pancreas divisum will not be*
654 *considered to be a causative factor for the pancreatitis episode. If imaging is not able to discriminate between gall bladder*
655 *polyps or concrements, lesions smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm,*
656 *irrespective of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and these patients*
657 *will be excluded from PICUS. ALT = alanine transaminase. CBD = common bile duct. ERCP = endoscopic retrograde*
658 *cholangiopancreatography.*

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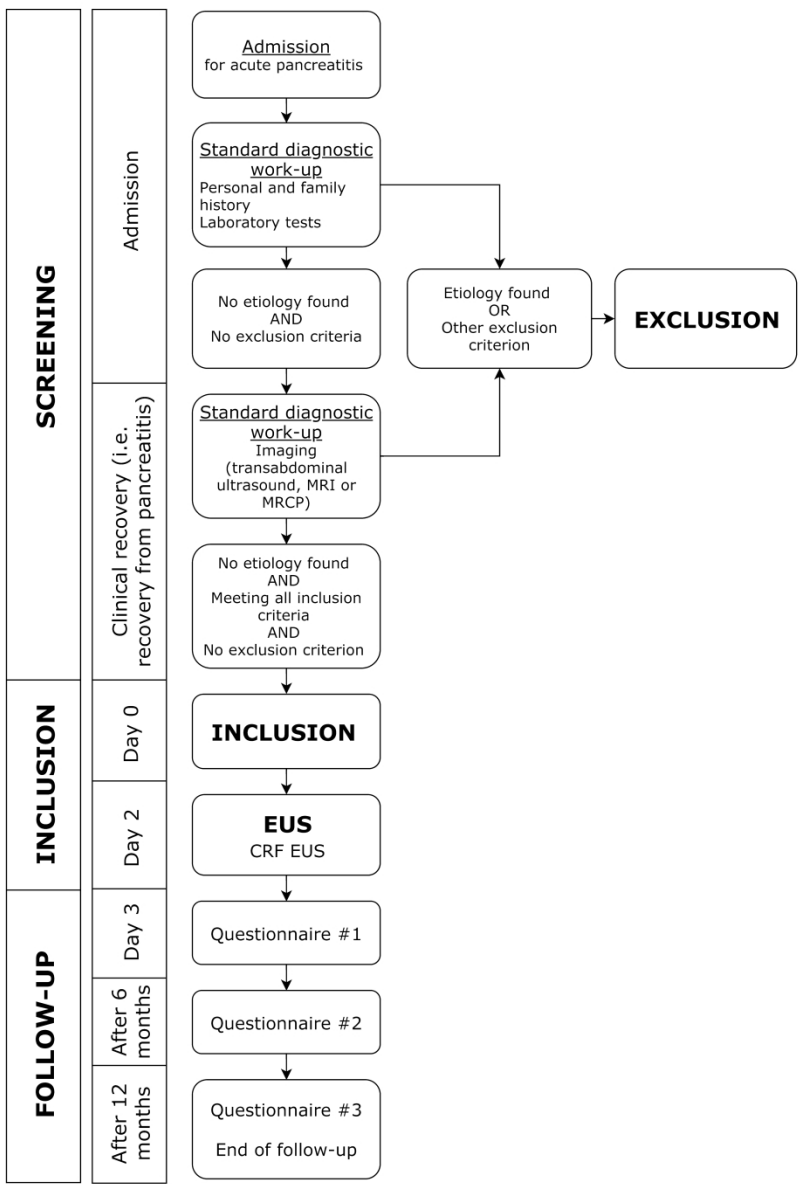
666 Table 3

<i>Biliary pancreatitis</i>	Presence of biliary stones, microlithiasis, or sludge
	Widened CBD, >8 mm in patients <76 years, or >10 mm in patients >75 years, in the absence of other CBD dilating factors (e.g. opioid use, distal stenosis, obstruction of external compression of CBD or papilla (67))
<i>Chronic pancreatitis</i>	Pancreatic calcifications
	> 4 of the following abnormal features of the pancreas: <ol style="list-style-type: none"> 1. Enlarged gland size 2. Cysts 3. Echo-poor lesions (focal areas of reduced echogenicity) 4. Echo-rich lesions (> 3 mm in diameter) 5. Accentuation of lobular pattern 6. Increased duct wall echogenicity 7. Irregularity of the main pancreatic duct 8. Dilation of the main pancreatic duct > 3.5 mm (68) 9. Visible side branches 10. Calcifications of the pancreatic duct
<i>Neoplasms</i>	Definitive diagnosis of pathological tissue after histological or cytological evaluation of specimen of an anomaly observed during EUS, e.g. hyperplastic or malignant tissue, or auto-immune inflammatory disease
	Main duct IPMN or mixed type IPMN causing dilatation of the pancreatic duct

667 **Table 3: positive imaging** Definition of positive imaging. For each diagnosis, presence of one of the separately mentioned
 668 abnormalities is required to be considered as positive imaging. Specimen is not required to be obtained during EUS. Anatomical
 669 anomalies (e.g. divisum) are not considered a certain etiology in first episode IAP and therefore not considered as positive
 670 imaging. CBD = common bile duct. EUS = endoscopic ultrasonography. IPMN = intraductal papillary mucinous neoplasm.

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Overview of screening and study procedures. MRI = magnetic resonance imaging. MRCP = magnetic resonance cholangiopancreatography. CRF = Case Report Form. EUS = endoscopic ultrasonography.

105x154mm (1200 x 1200 DPI)

Additional file 1: Table S1 Drugs associated with acute pancreatitis

Drugs associated with acute pancreatitis				
Acetaminophen	Cisplatin	Hydrochlorothiazide	Methyldopa	Pentavalent antimony compounds
Asparaginase	Cytarabine	Interferon alpha	Metronidazole	
Azathioprine	Didanosine	Itraconazole	Octreotide	Phenformin
Bortezomib	Enalapril	Lamivudine	Olanzapine	Simvastatin
Capecitabine	Erythromycin	Mercaptopurine	Opiates	Steroids
Carbamazepine	Estrogens	Mesalazine	Oxyphenbutazone	Sulfasalazine
Cimetidine	Furosemide	Olsalazine	Pentamidine	co-trimoxazole

Drugs with a definite association with acute pancreatitis (1, 2)

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1 Additional file 2: Relevant definitions

2 Acute pancreatitis: an acute inflammation of the pancreatic parenchyma, diagnosed when at least two
3 of the three following characteristics are present (1):

- 4 1. Clinical features of acute pancreatitis, such as upper abdominal pain
- 5 2. Elevated serum amylase or lipase levels of at least three times the upper limit of normal (ULN)
- 6 3. Signs of acute pancreatitis on imaging

7 Note: no value of the required serum amylase or lipase level is provided as every participating center
8 has a local laboratory, which is why each center may use different normal range values.

9
10 Idiopathic acute pancreatitis is considered to be present if no etiology is found in standard work-up,
11 according to the IAP/APA evidence-based guidelines on management of acute pancreatitis (2), which
12 comprises at least the following tests:

- 13 1. A detailed personal and family history, including questions on:
 - 14 a. Alcohol use
 - 15 b. Recent endoscopic retrograde cholangiopancreatography (ERCP)
 - 16 c. Recent start of or changes in use of drugs associated with acute pancreatitis
 - 17 d. Recent major abdominal trauma
 - 18 e. Recent abdominal surgery
 - 19 f. Familial pancreatitis
 - 20 g. Hereditary pancreatitis

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3 21 h. Cystic fibrosis related pancreatitis
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6 22 2. Laboratory tests, including:
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9 23 a. Blood serum triglycerides level on admission
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11 24 b. Blood serum calcium level, corrected for the serum albumin level, on admission
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14 25 c. Blood serum alanine transaminase (ALT) level on admission
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16

17 26 3. Imaging via transabdominal ultrasound, magnetic resonance imaging (MRI) or magnetic
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20 27 resonance cholangiopancreatography (MRCP) after clinical recovery
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23 28 Note: side branch or mixed type intraductal papillary mucinous neoplasms (IPMN) without dilatation
24
25 29 of the pancreatic duct will not be considered to be a causative factor for the pancreatitis episode.
26
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28 30 Note: if the imaging is not able to discriminate between gall bladder polyps or concrements, lesions
29
30 31 smaller than 10 mm will not be considered an exclusion criterion. Lesions above 10 mm, irrespective
31
32 32 of whether they are a polyp or a concrement, are an immediate indication for cholecystectomy, and
33
34 33 will be excluded from PICUS.
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40 35 Alcoholic pancreatitis: pancreatitis caused by an excess intake of alcohol, diagnosed when biliary
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42 36 etiology is not demonstrated by standard work-up and the patient has indicated (either by direct or
43
44 37 indirect personal history or by findings during physical examination) to have drunk at least five units of
45
46 38 alcohol in the 24 hours prior to start of abdominal complaints (or in asymptomatic acute pancreatitis:
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48 39 prior to diagnosis) (3-5)
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3 42 Biliary pancreatitis: pancreatitis caused by biliary stones, microlithiasis or sludge, diagnosed when one
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5 43 of the following features is present:

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8 44 1. A transient elevated ALT level of more than two times the ULN at diagnosis of acute
9
10 45 pancreatitis, in the absence of ALT elevating comorbidity (6)
11
12
13 46 2. Signs of presence of gallstones, microlithiasis or sludge on imaging, defined as follows:
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16 47 a. Gallstones, microlithiasis and/or biliary sludge, either in the gall bladder, ductus
17
18 48 cysticus, intrahepatic bile ducts or in the common bile duct (CBD), and/or
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20
21 49 b. A CBD of more than eight mm in patients 75 years old or younger or more than ten
22
23 50 mm in patients older than 75 years at diagnosis of acute pancreatitis (7)

24
25
26 51 Note: no value of the required serum ALT level is provided as the normal range values depend on the
27
28 52 sex of the patient and as every participating center has a local laboratory, which is why each center
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30 53 may use different normal range values.
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37 55 Chronic pancreatitis: a chronic inflammation of the pancreatic parenchyma, defined as typical clinical
38
39 56 history of chronic pancreatitis (such as recurrent pancreatitis or abdominal pain, except for primary
40
41 57 painless pancreatitis) and one or more of the following (8):

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43
44 58 1. Pancreatic calcifications
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46
47 59 2. Moderate or marked ductal lesions, defined as two or more of the following abnormal features
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49 60 on transabdominal ultrasound, computed tomography (CT) or MRI/MRCP, according to the
50
51 61 Cambridge classification (9):
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54 62 a. Main pancreatic duct abnormalities, either enlargement or increased echogenicity of
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56 63 the duct wall (mandatory)
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59 64 b. Pancreatic enlargement
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3 65 c. Cavities
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- 6 66 d. Duct irregularities including intraductal fillings defects, calculi or duct obstruction
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- 9 67 e. Focal acute pancreatitis
10
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- 12 68 f. Parenchymal heterogeneity
13
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- 15 69 g. Irregularities of pancreatic head or body contour
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- 18 70 3. Moderate or marked ductal lesions, defined as five or more of the following abnormal features
19
20 71 on endoscopic ultrasonography (EUS):
21
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- 23 72 a. Enlarged gland size
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25
- 26 73 b. Cysts
27
28
- 29 74 c. Echo-poor lesions (focal areas of reduced echogenicity)
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- 32 75 d. Echo-rich lesions (more than three mm in diameter)
33
34
- 35 76 e. Accentuation of lobular pattern (e.g., echo-poor normal parenchyma surrounded by
36
37 77 hyperechoic strands)
38
39
- 40 78 f. Increased duct wall echogenicity
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- 43 79 g. Irregularity of the main pancreatic duct (e.g., with narrowing of the duct)
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- 46 80 h. Dilation of the main pancreatic duct
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- 49 81 i. Visible side branches (e.g., with dilation)
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- 52 82 j. Calcification (of the pancreatic duct)
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- 55 83 4. Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly
56
57 84 reduced by enzyme supplementation
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- 60 85 5. Typical histology of an adequate histological specimen

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3 86 Note: during initial diagnostic work-up during admission 'marked and persistent exocrine insufficiency'
4
5 87 cannot be evaluated properly. Therefore this part of the definition of chronic pancreatitis will not be
6
7 88 applicable during standard work-up. However, if the patient does show marked and persistent
8
9 89 exocrine insufficiency during follow-up (either during the outpatient clinic visit after repeat
10
11 90 transabdominal ultrasound or after the EUS), this will be considered to be diagnostic for chronic
12
13 91 pancreatitis. The same is applicable for histology of an adequate histological specimen: this is not part
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15 92 of standard work-up, however, if a typical histological specimen is obtained during follow-up, this will
16
17 93 be considered to be diagnostic for chronic pancreatitis.
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24 95 Clinical recovery from acute pancreatitis: resolution of pancreatic inflammation, present when one of
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26 96 the following criteria is met:

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29 97 1. Discharge from the hospital
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32 98 2. Normal inflammation parameters in laboratory tests
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35 99 3. No signs of pancreatic inflammation on imaging
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41 101 Cystic fibrosis: an autosomal recessive disorder caused by a mutation in the CFTR gene, resulting in
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43 102 defective chloride channels in epithelial cells, diagnosed by either a concentration in sweat of chloride
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45 103 greater than 60 mmol/L on repeated analysis, confirmation of a CFTR gene mutation, or both (10).
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51 105 Cystic fibrosis related pancreatitis: pancreatitis caused by defective ductular and acinar pancreatic
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53 106 secretion, diagnosed when a patient with a history of cystic fibrosis presents with an acute pancreatitis
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55 107 in the absence of another origin (10).
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3 109 Familial pancreatitis: acute pancreatitis from any cause that occurs in a family with an incidence that
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5 110 is greater than would be expected by chance alone, given the size of the family and the standardized
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7 111 incidence of pancreatitis within the Dutch population, defined as acute pancreatitis in patients who
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9 112 have two or more direct blood-related family members (parents, children or siblings) who have had an
10
11 113 episode of acute pancreatitis (11-13).

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18 115 Fever: a body temperature of 38.5°C or higher.

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24 117 Hereditary pancreatitis: otherwise unexplained pancreatitis in an individual from a family in which the
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26 118 pancreatitis phenotype appears to be inherited through a disease-causing gene mutation expressed in
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28 119 an autosomal dominant pattern, defined as pancreatitis in patients with a known mutation in the
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30 120 PRSS1 gene, the SPINK1 gene, the CFTR gene, the CTSC gene, the CLDN2 gene or the CPA1 gene, or if
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32 121 the patient has a direct family member (parents, children, siblings) with one or more of the above
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34 122 mentioned mutations and has at least one direct family member who has had an episode of acute
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36 123 pancreatitis or has chronic pancreatitis (13, 14).

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43 125 Hypercalcemic pancreatitis: acute pancreatitis caused by hypercalcemia and diagnosed when no signs
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45 126 of a biliary pancreatitis are found in standard work-up and the patient has a blood serum calcium level
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47 127 of at least 12 mg/dl or 3 mmol/l, corrected for the serum albumin level, as first measured during
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49 128 admission (15).

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3 131 Hypertriglyceridemic pancreatitis: acute pancreatitis based on hypertriglyceridemia and diagnosed if
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5 132 a biliary etiology is not demonstrated by standard work-up and the patient has a blood serum
6
7 133 triglyceride level of at least 1000 mg/dl (or 11.2 mmol/l) under fasting conditions, as first measured
8
9 134 during admission (16).
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15 136 Hypothermia: a body temperature of 35.9°C or lower.
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21 138 Infected (extra)pancreatic necrosis: presence of microorganisms in (extra-)pancreatic necrosis,
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23 139 confirmed by a positive culture obtained by means of fine needle aspiration or from the first drainage
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25 140 procedure or necrosectomy, the presence of gas in the (extra-)pancreatic collection on CT, or the
26
27 141 presence of clinical signs of persistent sepsis or progressive clinical deterioration despite maximal
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29 142 support on the intensive care unit (ICU) without other causes for infection (ruled out should be:
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31 143 pneumonia, urinary tract infection, wound infection, endocarditis, abdominal sepsis or any other
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33 144 infection which could be suspected based on the individual patient's clinical presentation) (17).
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40 146 Medication associated pancreatitis: acute pancreatitis is considered to be caused by drugs when a
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42 147 biliary cause is not demonstrated by standard work-up, the patient uses one or multiple drug(s) listed
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44 148 in table S1 in additional file 1, the drug has been started or increased in dosage within a reasonable
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46 149 temporal sequence, in principle 1 month before the onset of the pancreatitis, and has a positive
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48 150 dechallenge (a drug reaction that is confirmed by stopping the drug) (18, 19).
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54 152 Microlithiasis: stones or concrements, smaller than four mm, in the gall bladder or the bile ducts (20).
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3 154 Murphy's sign: the phenomenon where compression of the right upper quadrant causes the patient
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5 155 to catch their breath due to pain when taking a deep breath (21).
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11 157 Pancreas divisum: a congenital malformation of the main pancreatic duct (Wirsung's duct) with two
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13 158 separate ducts (a separate ventral duct of Wirsung and a dorsal duct of Santorini) as opposed to one
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15 159 main duct (of Wirsung) (22).
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21 161 Positive imaging: positive imaging is defined as imaging during which a definitive cause for the acute
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23 162 pancreatitis episode can be found; or during which abnormalities are visualized constituting a
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25 163 definitive cause, after obtaining tissue and pathological examination. So, if during EUS ductal
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27 164 abnormalities are found, yet not enough to make a certain diagnosis of chronic pancreatitis according
28
29 165 to the M-ANNHEIM classification (8), this imaging is considered to be negative, even though it did show
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31 166 abnormalities. This approach is chosen because the aim of this study is to determine the rate of which
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33 167 EUS can find a causative factor for a previous acute pancreatitis episode. For the same reason, finding
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35 168 of an anatomical abnormality after a first episode of acute pancreatitis is not scored as positive
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37 169 imaging. An overview of the exact findings scored as positive imaging is provided in table 3 of the main
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39 170 manuscript.
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172 Post-ERCP pancreatitis: pancreatitis caused by mechanical injury from instrumentation and hydrostatic
173 injury from contrast injection during ERCP, diagnosed if a patient develops a pancreatitis within 24
174 hours of an ERCP without indications of another origin (23).
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3 176 Postoperative pancreatitis: pancreatitis caused by perioperative hypoperfusion of the pancreas,
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5 177 diagnosed if a patient develops a pancreatitis within 24 hours of abdominal surgery in the absence of
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7 178 indications for another origin (24).
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13 180 Posttraumatic pancreatitis: pancreatitis caused by pancreatic injury due to trauma to the abdomen,
14
15 181 diagnosed when the patient describes a typical blunt trauma to the upper abdomen and pancreatic
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17 182 trauma is visible on imaging (25).
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23 184 Recurrence rate: the risk of a recurrent episode of acute pancreatitis.
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29 186 Sludge: solid material which results from the slow settling of particles dispersed in bile (20).
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3 197 Standard work-up:
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6 198 1. A detailed personal and family history, including questions on:
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9 199 a. Alcohol use
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12 200 b. Recent ERCP
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15 201 c. Recent start of or changes in use of drugs associated with acute pancreatitis
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18 202 d. Recent major abdominal trauma
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21 203 e. Recent abdominal surgery
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24 204 f. Familial pancreatitis
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27 205 g. Hereditary pancreatitis
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30 206 h. Cystic fibrosis related pancreatitis
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32 207 2. Laboratory tests, including:
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35 208 a. Blood serum triglycerides level, first measured during admission
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38 209 b. Blood serum calcium level, corrected for the serum albumin level, first measured
39 during admission
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43 211 c. Blood serum ALT level on admission
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46 212 3. Imaging via transabdominal ultrasound, MRI or MRCP after clinical recovery
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52 214 Biliary events: acute cholecystitis; biliary colic's requiring readmission; biliary pancreatitis; cholangitis;
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54 215 or obstructive choledocholithiasis needing ERCP.
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3 217 Acute cholecystitis: an acute inflammation of the gall bladder, diagnosed when one item in A, B and C

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5 218 is present:

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8 219 A) Local signs of inflammation

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11 220 1. Murphy's' sign, or

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14 221 2. Right upper abdominal quadrant mass, pain or tenderness

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17 222 B) Systemic signs of inflammation

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20 223 1. Fever or hypothermia, or

21
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23 224 2. Elevated C-reactive protein (CRP), or

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25
26 225 3. Elevated white blood cell count

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29 226 C) Imaging findings characteristic of acute cholecystitis (26, 27)

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31 227 Note: acute cholecystitis and cholangitis (see definition below) are defined according to the Tokyo
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33 228 classification which defines fever as a body temperature of 38°C or higher; however, fever will be
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35 229 defined in this study as hyperthermia of 38.5°C or higher and hypothermia will be added as a systemic
36
37 230 sign of inflammation, as this more accurately reflects clinical practice in the Netherlands.

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44 232 Biliary colic: upper abdominal pain (either right upper quadrant or epigastric pain) lasting at least 30
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46 233 minutes, often associated with restlessness (28).

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3 238 Cholangitis: an inflammation of the bile duct(s), diagnosed when one item in each of the following
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5 239 categories is present:

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8 240 1. Systemic inflammation

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11 241 a. Fever, hypothermia and/or shaking chills

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13
14 242 b. Laboratory data: evidence of inflammatory response (abnormal white blood cell
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16 243 counts (defined as smaller than 4,000/ μ l or larger than 10,000/ μ l), increase of serum
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18 244 CRP levels (defined as 1 mg/dl or higher), and other changes indicating inflammation)

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21 245 2. Cholestasis

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24 246 a. Jaundice (defined as a total bilirubin of 2 mg/dl or higher)

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27 247 b. Laboratory data: abnormal liver function tests (increased serum alkaline phosphatase,
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29 248 gamma-glutamyltransferase (gamma-GT), aspartate transaminase (AST) and ALT
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31 249 levels (defined as more than 1.5 times the ULN))

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34 250 3. Imaging

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37 251 a. Biliary dilatation

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40 252 b. Evidence of the etiology on imaging (stricture, stone, stent etc.) (26)

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46 254 Obstructive choledocholithiasis: presence of gallstones, microlithiasis or biliary sludge in the CBD on
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48 255 imaging, requiring an ERCP, according to the treating physician.

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284 [I&HD=180221-1109&HDR=G1&STB=T](http://statline.cbs.nl/Statweb/publication/?VW=T&DM=SLNL&PA=37312&D1=a&D2=0,5,10,(1-2)-&HD=180221-1109&HDR=G1&STB=T).

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Additional file 3: Short Form 36 Questionnaire

English version

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1. In general, would you say your health is:
- excellent
 - very good
 - good
 - fair
 - poor
2. **Compared to one year ago**, how would you rate your health in general **now**?
- much better now than one year ago
 - somewhat better now than one year ago
 - about the same
 - somewhat worse now than one year ago
 - much worse now than one year ago

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3 3. The following items are about activities you might do during a typical day.
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5 Does **your health now limit you** in these activities? If so, how much?
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	Yes, limited a lot	Yes, limited a little	No, not limited at all
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4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

- | | Yes | No |
|--|--------------------------|--------------------------|
| a. Cut down the amount of time you spent on work or other activities | <input type="checkbox"/> | <input type="checkbox"/> |
| b. Accomplished less than you would like | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Were limited in the kind of work or other activities | <input type="checkbox"/> | <input type="checkbox"/> |
| d. Had difficulty performing the work or other activities (for example, it took extra effort) | <input type="checkbox"/> | <input type="checkbox"/> |

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- | | Yes | No |
|---|--------------------------|--------------------------|
| a. Cut down the amount of time you spent on work or other activities | <input type="checkbox"/> | <input type="checkbox"/> |
| b. Accomplished less than you would like | <input type="checkbox"/> | <input type="checkbox"/> |
| c. Didn't do work or other activities as carefully as usual | <input type="checkbox"/> | <input type="checkbox"/> |

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6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

not at all
 slightly
 moderately
 quite a bit
 extremely

7. How much **bodily** pain have you had during the **past 4 weeks**?

none
 very mild
 mild
 moderate
 severe
 very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

not at all
 a little bit
 moderately
 quite a bit
 extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks ...	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Have you been a very nervous person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Have you felt calm and peaceful?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Did you have a lot of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Have you felt downhearted and blue?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Did you feel worn out?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Have you been a happy person?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Did you feel tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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10. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?
- all of the time
- most of the time
- some of the time
- a little of the time
- none of the time

11. How TRUE or FALSE is **each** of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. I am as healthy as anybody I know.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. I expect my health to get worse.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. My health is excellent.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Space for additional remarks with the questionnaire:

Dutch version

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1. Wat vindt u, over het algemeen genomen, van uw gezondheid?
- uitstekend
 - zeer goed
 - goed
 - matig
 - slecht
2. In vergelijking met 1 jaar geleden, hoe zou u nu uw gezondheid in het algemeen beoordelen?
- veel beter dan een jaar geleden
 - iets beter dan een jaar geleden
 - ongeveer hetzelfde als een jaar geleden
 - iets slechter dan een jaar geleden
 - veel slechter dan een jaar geleden

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3. De volgende vragen gaan over dagelijkse bezigheden. Wordt u door uw **gezondheid op dit moment** beperkt bij deze bezigheden? Zo ja, in welke mate?

	Ja, ernstig	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. <i>Forse inspanning</i> (zoals hardlopen, zware voorwerpen tillen, inspannend sporten)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. <i>Matige inspanning</i> (zoals het verplaatsen van een tafel, stofzuigen, fietsen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Tillen of boodschappen dragen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. <i>Een paar</i> trappen oplopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. <i>Eén</i> trap oplopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Buigen, knielen of bukken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. <i>Meer dan een kilometer</i> lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Een halve kilometer lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. <i>Honderd meter</i> lopen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
j. Uzelf wassen of aankleden	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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4. Had u, ten gevolge van uw **lichamelijke gezondheid**, *de afgelopen 4 weken* één van de volgende problemen bij uw werk of andere bezigheden?

Ja

Nee

a. U heeft *minder tijd* kunnen besteden aan werk of andere bezigheden.

b. U heeft *minder bereikt* dan u zou willen.

c. U was beperkt in het *soort* werk of soort bezigheden.

d. U had moeite met het werk of andere bezigheden (het kostte u bijvoorbeeld extra inspanning).

5. Had u, ten gevolge van een **emotioneel probleem** (bijvoorbeeld doordat u zich depressief of angstig voelde), *de afgelopen 4 weken* één van de volgende problemen bij uw werk of andere bezigheden?

Ja

Nee

a. U heeft *minder tijd* kunnen besteden aan werk of andere bezigheden.

b. U heeft *minder bereikt* dan u zou willen.

c. U heeft het werk of andere bezigheden niet zo zorgvuldig gedaan als u gewend bent.

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6. In hoeverre heeft uw **lichamelijke gezondheid** of hebben uw **emotionele problemen** u *de afgelopen 4 weken* belemmerd in uw normale sociale bezigheden met gezin, vrienden, buren of anderen?
- helemaal niet
 enigszins
 nogal
 veel
 heel erg veel
7. Hoeveel **pijn** had u *de afgelopen 4 weken*?
- geen
 heel licht
 licht
 nogal
 ernstig
 heel ernstig
8. In welke mate heeft **pijn** u *de afgelopen 4 weken* belemmerd bij uw normale werkzaamheden (zowel werk buitenshuis als huishoudelijk werk)?
- helemaal niet
 enigszins
 nogal
 veel
 heel erg veel

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12. De volgende vragen gaan over hoe u zich *de afgelopen 4 weken* heeft **gevoeld**. Wilt u bij elke vraag het antwoord aankruisen dat het beste aansluit bij hoe u zich heeft gevoeld?

Hoe vaak
gedurende *de*
afgelopen 4
weken:

Voortdurend **Meestal** **Vaak** **Soms** **Zelden** **Nooit**

- | | | | | | | | |
|----|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| a. | voelde u zich levenslustig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| b. | voelde u zich erg zenuwachtig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| c. | zat u zo erg in de put dat niets u kon opvrolijken? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| d. | voelde u zich kalm en rustig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| e. | voelde u zich erg energiek? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| f. | voelde u zich neerslachtig en somber? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| g. | voelde u zich uitgeblust? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| h. | voelde u zich gelukkig? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| i. | voelde u zich moe? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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10. *Hoe vaak* hebben uw **lichamelijke gezondheid of emotionele problemen** gedurende *de afgelopen 4 weken* uw sociale activiteiten (zoals bezoek aan vrienden of naaste familieleden) belemmerd?
- voortdurend
 meestal
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11. Wilt u het antwoord kiezen dat het beste weergeeft hoe juist of onjuist u elk van de volgende uitspraken voor uzelf vindt?

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	Volkomen juist	Grotendeels juist	Weet ik niet	Grotendeels onjuist	Volkomen onjuist
a. Ik lijk gemakkelijker ziek te worden dan andere mensen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Ik ben net zo gezond als andere mensen die ik ken.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Ik verwacht dat mijn gezondheid achteruit zal gaan.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Mijn gezondheid is uitstekend.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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Ruimte voor aanvullende opmerkingen bij de vragenlijst: