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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Schepers NJ, Hallensleben NDL, Besselink MG, et al. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *Lancet* 2020; **396:** 167–76.

SUPPLEMENTARY APPENDIX

Supplement to manuscript:

Urgent ERCP with sphincterotomy or conservative treatment in gallstone pancreatitis (APEC): a multicentre randomised controlled trial

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The trial protocol is published in *Trials.* 2016 Jan 5;17:5 (Open Access).

Content

Additional information

Methods

Inclusion criteria

The following criteria were used in addition to the inclusion criteria mentioned in the main manuscript.

- Ability to perform ERC within 24 hours after presentation to the emergency department and no more than 72 hours after symptom onset
- In case of a previous episode of necrotising pancreatitis, patient had to be be fully recovered (confirmed on imaging)
- Age ≥18 years
- Written informed consent

Exclusion criteria

The following criteria were used in addition to the exclusion criteria mentioned in the main manuscript.

- Pancreatitis due to other causes such as alcohol abuse (more than 4 units per day), metabolic causes (hypertriglyceridemia or hypercalcemia), medication, trauma, etc.
- International Normalized Ratio that cannot be corrected to less than 1.5 with clotting factors or fresh frozen plasma
- Pregnancy

Randomisation

At randomization patients were stratified for the presence of cholestasis and for the region of the hospital. The 26 hospitals were divided into 5 regions: one region including all academic hospitals and the other 4 regions consisted of non-academic hospitals according to geographical location.

General supportive treatment regimen

Both study groups were treated with intravenous infusion of fluids to ensure adequate hydration and diuresis, appropriate analgesic treatment, enteral nutrition, if necessary, treatment of endocrine and exocrine pancreatic insufficiency, and a gastric tube in case of vomiting. The need for intensive care monitoring or treatment was left at the discretion of the treating physician. A contrast-enhanced CT (CECT) was performed 5 to 7 days after hospital admission for assessment of pancreatic parenchymal necrosis. In case a patient was discharged within 5 days, no

routine CECT was performed and the disease course was considered mild.

An elective ERCP was performed in case of persistent cholestasis or retained bile duct stones when the patient had recovered from the initial pancreatitis episode. In the case of incomplete stone extraction, a plastic endoprosthesis was inserted, and a repeat ERCP was scheduled electively. During ERCP, antibiotics were only administered in case of contrast injection without adequate biliary drainage. The timing of cholecystectomy was not defined in the trial protocol.

Endpoints

Secondary endpoints included the need and length of intensive care admission, the length of hospital stay, readmissions for biliary events, quality of life and costs. The quality of life data were gathered with the SF-36, and analyzed as repeated measures by linear mixed modelling.[1] The association of treatment with PCS and MCS were evaluated with a linear mixed effects models in which we considered time as a factor (with levels 0 months, 3 months and 6 months). To take into account that repeated measurements of the same patients were not independent, we included subject specific (random) effects for the intercept and each time category. We additionally considered an interaction term between treatment and time and evaluated whether this interaction was needed using a likelihood ratio test. The likelihood ratio tests showed that there was no evidence of an interaction between time and treatment in either of the two models (p-values were 0.461 for PCS and 0.747 for MCS). Since the likelihood ratio test showed that there was no evidence for an interaction between the treatment arm and time, and interaction terms complicated the interpretation of the results, we presented the results of the model without the interaction term. Data on use of resources were gathered with clinical report forms and the generic Health and Labour Questionnaire. Unit costing was done in accordance with the Dutch Costing Manual for health care research. Health utilities were derived from gathered EQ5D-5L health status questionnaire data and the existing Dutch health status valuation algorithm available from www.euroqol.org. The average health utility during follow-up, weighted for the lengths in weeks of preceding periods in between successive measurements and multiplied by one half (0.5) to reflect the time horizon of 180 days, was taken as the number of quality adjusted life years (QALY) a patient generated. In patients with missing QALY estimates, imputation was performed by assigning the mean QALY value of other patients in their allocated group, with or without cholestasis, and with or without occurrence of the primary outcome (eight strata). Results on costs, QALYs and differences between treatment groups are reported with bias-corrected and accelerated 95% confidence intervals (BCa 95% CI) to account for sampling variability, based on bootstrapping of 5,000 samples. The bootstrap results are reported with quadrants of the incremental

costs versus the numbers of patients with poor outcome prevented or versus the numbers of QALYs gained. Further, a cost-effectiveness acceptability curve is shown reflecting the probability of urgent ERCP with sphincterotomy being cost-effective compared with conservative treatment for levels of willingness to pay per QALY up to €100,000.

Statistical analysis

Primary analysis, using the Pearson's Chi-squared test without continuity correction, was based on the intention-to-treat principle, with patients being analyzed according to original treatment allocation, regardless of whether the cannulation or sphincterotomy was successful. Data is presented as relative risks with 95 % confidence intervals. A two-tailed $P < 0.05$ was considered statistically significant. Individual components of the primary endpoint and secondary endpoints were compared between treatment arms using the Pearson's chi-squared test or the Fisher exact test, as appropriate. Relative risks with 95% confidence intervals are presented. Length of hospital stay, difficulty of cholecystectomy, intensive care stay and number of endoscopic, radiological and operative (re-)interventions were compared between treatment arms using the Mann-Whitney U test. The following secondary endpoints were compared using the Pearson's chi-squared test: need for intensive care admission, ERCP related complications, respiratory complications after randomization, readmission for biliary events (recurrent ABP, cholecystitis, biliary colics, cholangitis). In the economical evaluation: costs were compared between treatment arms using samples t-tests. Predefined exploratory subgroup analysis was according to the presence of cholestasis. Logistic regression models were used to test whether treatment effects differ significantly between these subgroups. An interim analysis of the primary endpoint was performed after 50% of patients were randomised and discharged from the hospital. The Haybittle-Peto approach was used for beneficial effect, meaning that the trial would have been ended using symmetric stopping boundaries at a P value of less than 0.001.[2,3] The trial would not be stopped for futility.

Results

Five of 117 patients (4%) did not undergo urgent ERCP: two patients refused an ERCP after randomization, one patient severely deteriorated in the hours prior to ERCP and in two patients urgent ERCP was postponed due to logistic reasons and ultimately cancelled because the condition of the patient improved.

The mean societal costs per patient during admission after 6 months follow-up was € 24,627 ($ 27,892) for the urgent ERCP with sphincterotomy group compared with € 24,595 ($27,856) in the conservative group; a mean

difference of € 32 ($ 36) in favour of the conservative group (BCa 95% CI -€13,030 to €10,845; P=0.994). Patients in the urgent ERCP with sphincterotomy group generated on average 0.3524 QALYs (BCa 95% CI: 0.3268 to 0.3766) versus a mean of 0.3195 QALYs (BCa 95% CI: 0.2880 to 0.3505) per patient in the conservative group. The difference of 0.0329 QALYs was in favour of the urgent ERCP with sphincterotomy group (BCa 95% CI: -0.0079 to 0.0729; P=0.11).

We observed more intensive care admissions in the urgent ERCP with sphincterotomy group: 24 patients (21%) in the urgent ERCP group versus 13 patients (12%) in the conservative group (P = 0.06). In the urgent ERCP group, 10 of 24 patients were admitted to the intensive care unit within 48 hours after presentation. Of these 10 patients with early intensive care admissions, 7 patients were admitted because of organ failure at presentation (and before ERCP) or for monitoring during ERCP.

Box S1 Definitions of primary and secondary endpoints

Event	Definition
New-onset organ failure	New-onset (i.e. not present at randomisation) and persistent (i.e. >48 hours) failure of organ(s) according to the modified Marshall score [4,5].
Pancreatic necrosis	Presence of diffuse or focal areas of pancreatic non-enhancement on contrast enhanced CT performed at 5-7 days after admission.
Bacteremia	Demonstrated with positive blood cultures. For non-pathogens (e.g. Coagulase negative staphylococci) at least 2 samples have to be positive.
Cholangitis	Highest in-hospital body temperature in previous 24 hours: ≥ 38.5ºC with chills, without an obvious other cause (e.g., cystitis, pneumonia, thrombophlebitis, etc), **or** 39ºC without chills, without an obvious cause for fever, **and either:** 1) Choledocholithiasis on abdominal US, CT, EUS or MRI, **or** in the absence of gallstones and/or sludge 2) A dilated common bile duct on imaging defined as >8mm in patients ≤75 years or >10mm in patients >75 years **or** 3) Progressive cholestasis for at least two consecutive days and a bilirubin >2.3 mg/dL (40 µmol/L).
Pneumonia	Coughing, dyspnoea, chest film showing infiltrative abnormalities, lowered arterial blood gas with positive sputum culture. If in intensive care, a positive endotracheal culture is mandatory.
Exocrine pancreatic insufficiency	Fecal elastase <200µg/g and the need for pancreatic enzyme supplementation at 3 months after discharge; this requirement was not present before onset of pancreatitis.
Endocrine pancreatic insufficiency	The need for insulin or oral antidiabetic drugs at 3 months after discharge; this requirement was not present before onset of pancreatitis.
Recurrent biliary event	Biliary events (recurrent acute gallstone pancreatitis, cholecystitis, biliary colics, or cholangitis)

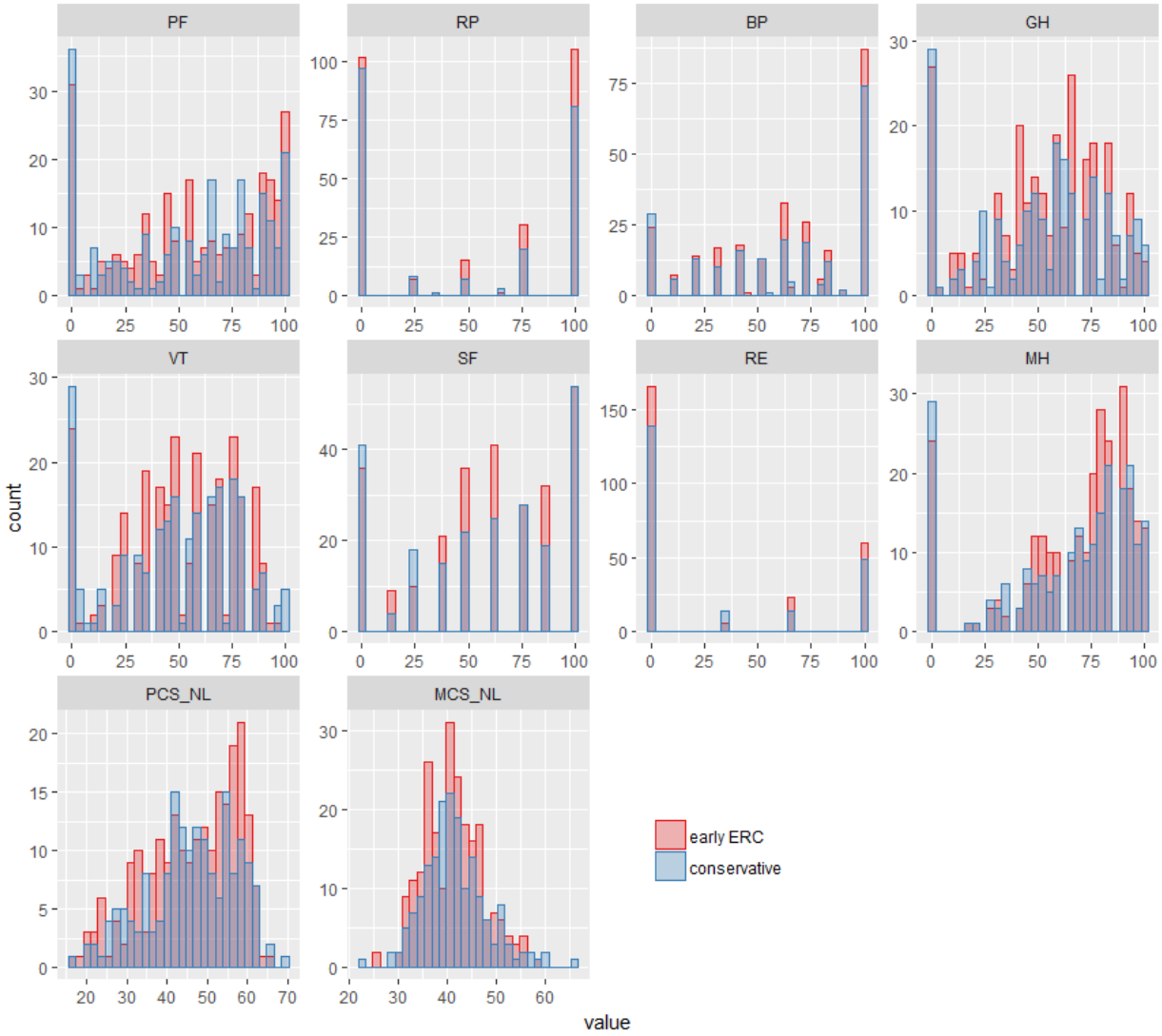
Box S2 Definitions of ERCP-related complications

Event	Definition
Clinically relevant bleed	The presence of melena, hematochezia or hematemesis, in combination with a hemoglobin drop of 1.3 mmol/L or the need for blood transfusion (defined according to the American Society for Gastrointestinal Endoscopy ASGE [6])
Perforation	New development of free gas on imaging with progressive complaints of abdominal discomfort and pain after ERCP, or perforation detected at surgery
Respiratory insufficiency	pO_2<60mmHg despite FiO_2 of 30% or requiring mechanical ventilation
Cardiovascular complications	
o Acute myocardial infarction	(1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms; (b) development of pathologic Q-waves on the ECG; (c) ECG changes indicative of ischemia (ST segment elevation or depression); or (d) coronary artery intervention (e.g., coronary angioplasty) [7,8].
o Cerebrovascular accident	Defined by the clinical event and subsequent findings on cross- sectional imaging investigations
o Shock	Systolic blood pressure below 90 mmHg despite adequate fluid resuscitation or need for inotropic catecholamine support

Figure S1 Quality of life analyses measured by SF-36

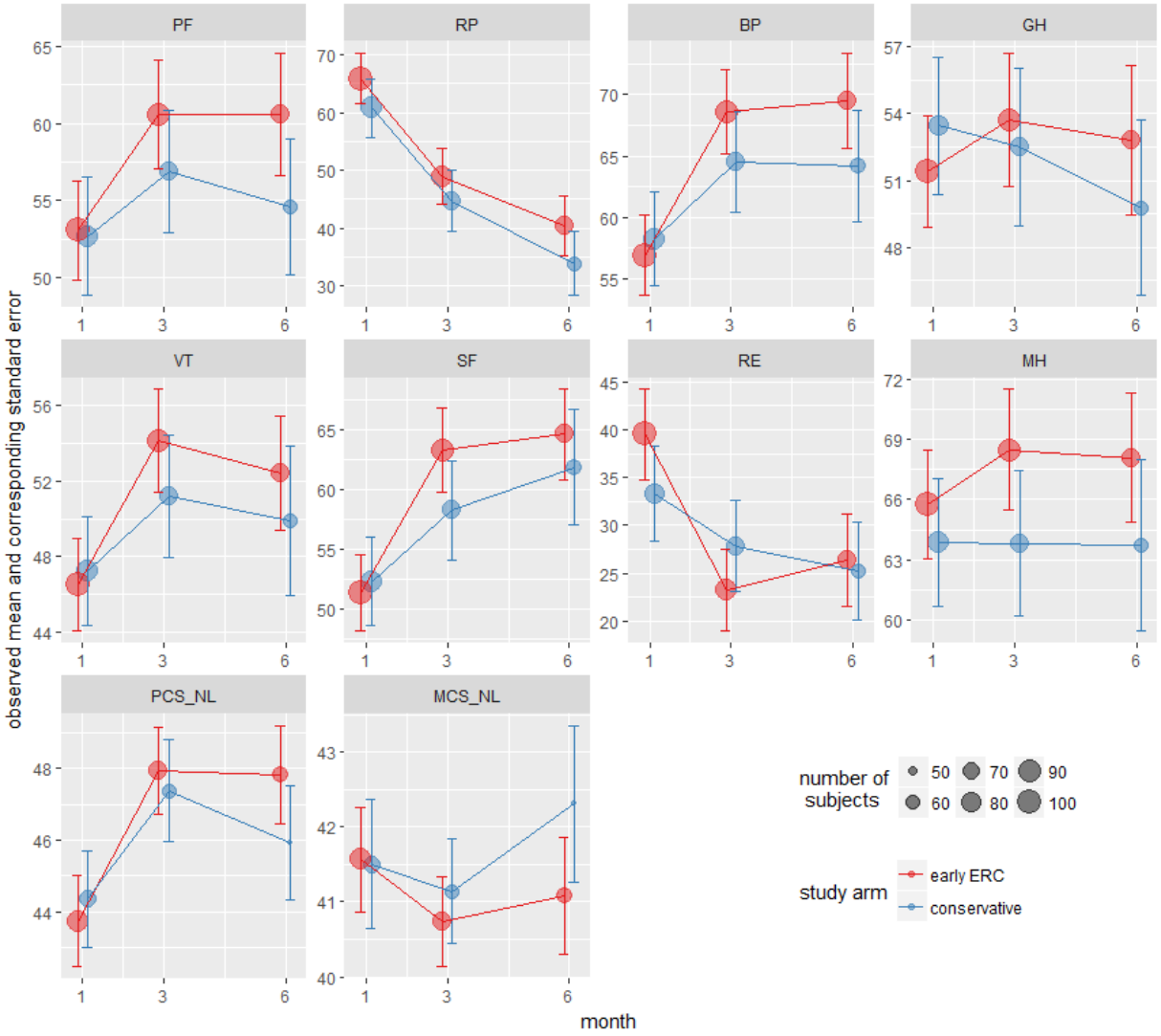
Figure S1A. Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the observed values at 1, 3 and 6 months after randomization.

Figure S1B. Health related quality of life measured by the 36-item Short Form Health Survey: distribution of the observed values across all time-points (1, 3 and 6 months) after randomization.



Note. PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health, PCS = physical component summary, MCS = mental component summary.

Figure 1B. Health related quality of life measured by the 36-item Short Form Health Survey: means, standards deviations and standard errors at 1, 3 and 6 months after randomization.



Note. PF = physical functioning, RP = role physical, BP = bodily pain, GH = general health, VT = vitality, SF = social functioning, RE = role emotional, MH = mental health, PCS = physical component summary, MCS = mental component summary. Data are presented as means with 95% confidence intervals at 1, 3 and 6 months after randomization.

Table S1. Health related quality of life measured by physical and mental component summary of the 36-item Short Form Health Survey

	Value	*Std.Error*	*DF*	*t-value*	*p-value*
Physical Component Summary					
• (Intercept)	43.828	1.260	232	34.778	0.000
• Urgent ERCP baseline	0.335	1.597	168	0.210	0.834
• Month 3 versus baseline	3.202	0.689	232	4.649	0.000
• Month 6 versus baseline	2.577	0.881	232	2.925	0.004
Mental Component Summary					
• (Intercept)	41.540	0.681	232	60.990	0.000
• Urgent ERCP baseline	-0.118	0.746	168	-0.158	0.875
• Month 3 versus baseline	-0.497	0.637	232	-0.780	0.436
• Month 6 versus baseline	0.288	0.667	232	0.431	0.667

Note. Analyzed as repeated measures by linear mixed modelling. N = number of patients with completed questionnaires, SD = standard deviation.

Table S2 Dutch unit costs (€) for resources used

Resources	Unit	Unit costs in 2017[#] (€)	Source
Index intervention			
Endoscopic retrograde cholangiography	Procedure	1,088.85	Tariff application
Major diagnostic costs and other therapeutic procedures			
All chemistry costs per admission day 1 to 7	Test	36.56	Tariff application
All chemistry costs per admission day > 7	Test	15.67	Tariff application
Blood culture	Test	29.36	Tariff application
Culture 1 medium (catheter tip)	Test	13.40	Tariff application
Culture <2 media (urine)	Test	18.13	Tariff application
Culture 2-3 media (sputum, ascites, drain)	Test	22.52	Tariff application
Abdominal ultrasound	Test	788.95	Tariff application
X-ray abdomen	Test	42.63	Tariff application
X-ray chest	Test	58.28	Tariff application
CT chest	Test	179.03	Tariff application
CT abdomen	Test	190.91	Tariff application
CT chest and abdomen	Test	369.94	Tariff application
MRCP / MRI bile ducts	Test	312.64	Tariff application
Abdominal diagnostic punction (fine needle aspiration)	Procedure	606.45	Tariff application
Percutaneous bile duct drainage	Procedure	381.78	Tariff application
Embolization	Procedure	1,504.68	Tariff application
Percutaneous catheter drainage abdominal collection	Procedure	425.38	Top-down costing
Percutaneous gallbladder drainage	Procedure	381.78	Tariff application
Endoscopic ultrasound	Procedure	788.95	Tariff application
Endoscopic transluminal drainage	Procedure	995.48	Top-down costing
Endoscopic transluminal necrosectomy	Procedure	1,099.83	Top-down costing
Laparoscopic cholecystectomy	Procedure	2,576.03	Tariff application
Open cholecystectomy	Procedure	3,997.81	Tariff application
Necrosectomy / VARD	Procedure	2,202.41	Top-down costing
Admission			
General ward academic center	Day	656.83	DMC 2015*
General ward non-academic center	Day	453.23	DMC 2015
Intensive care unit admission	Day	2,061.55	DMC 2015
Rehabilitation stay	Day	470.63	DMC 2015
Outpatient hospital care			
Medical specialist academic hospital	Visit	166.77	DMC 2015
Medical specialist non-academic hospital	Visit	81.85	DMC 2015
Emergency department	Visit	264.98	DMC 2015
Phone consultation academic hospital	Consultation	83.38	DMC 2015
Phone consultation general hospital	Consultation	40.92	DMC 2015
Out-of-hospital care			
General practitioner (GP)	Visit	33.76	DMC 2015
Physiotherapist	Visit	33.76	DMC 2015
Formal home care			
Alpha help	Hour	20.46	DMC 2015
Family support	Hour	23.53	DMC 2015
Out-of-pocket expenses			
Informal help	Hour	14.32	DMC 2015
Travel expenses hospital visit	Visit	4.43	DMC 2015
Travel expenses GP visit	Visit	3.28	DMC 2015
Travel expenses physiotherapist visit	Visit	3.50	DMC 2015
Productivity loss			
Per worker (non-specific for age or gender)	Working hour	34.75	DMC 2015

After price-indexing based on yearly general consumer price indices for the Netherlands.
*DCM 2015: Dutch Costing Manual for health care research.

Table S3 Mean use of resources by treatment strategy

	ERCP with sphincterotomy (N=117)	**Conservative treatment** (N=113)	**Difference ERCP minus conservative**
	Mean volume (BCa 95% CI)	**Mean volume** (BCa 95% CI)	**Mean volume** (BCa 95% CI)*
Hospital care			
ERCP with sphincterotomy	1.11 (1.03, 1.19)	0.50 (0.35, 0.69)	0.62 (0.36, 0.81)
Other procedures, *e.g.*:			
endoscopic	0.75 (0.46, 1.09)	0.70 (0.48, 0.96)	0.05 (-0.36, 0.49)
surgical	0.50 (0.42, 0.57)	0.51 (0.42, 0.60)	-0.02 (-0.17, 0.13)
radiological	5.37 (4.19, 6.65)	5.09 (3.86, 6.65)	0.28 (-1.86, 2.15)
various	1.59 (1.41, 1.78)	1.88 (1.60, 2.21)	-0.29 (-0.68, 0.07)
Inpatient stay	23.9 (19.4, 28.9)	22.0 (17.9, 27.3)	1.88 (-5.48, 8.86)
Outpatient treatment	5.28 (4.60, 5.97)	5.22 (4.57, 5.91)	0.06 (-0.94, 1.03)
Out-of-hospital care			
General practitioner	2.16 (1.75, 2.60)	1.73 (1.39, 2.07)	0.44 (-0.16, 1.07)
Physiotherapist	2.44 (1.34, 3.88)	1.81 (0.70, 3.55)	0.64 (-2.13, 2.88)
Formal home care			
Alpha help	2.56 (0.47, 5.21)	0.71 (0.00, 1.52)	1.86 (-0.39, 4.64)
Family support	4.36 (1.09, 8.56)	2.12 (0.64, 3.96)	2.24 (-1.68, 6.89)
Informal home care			
Family members^	51.8 (27.5, 84.4)	40.9 (22.7, 63.4)	11.0 (-23.6, 47.7)
Other volunteers^	4.58 (2.12, 7.49)	4.21 (1.20, 7.41)	0.37 (-4.74, 5.34)
Paid private help^	2.79 (1.32, 4.43)	4.35 (1.33, 7.98)	-1.57 (-6.49, 2.48)

* Testing for significant differences was done for costs, see Table EE3.
^ Costed with the unit costs of informal help.

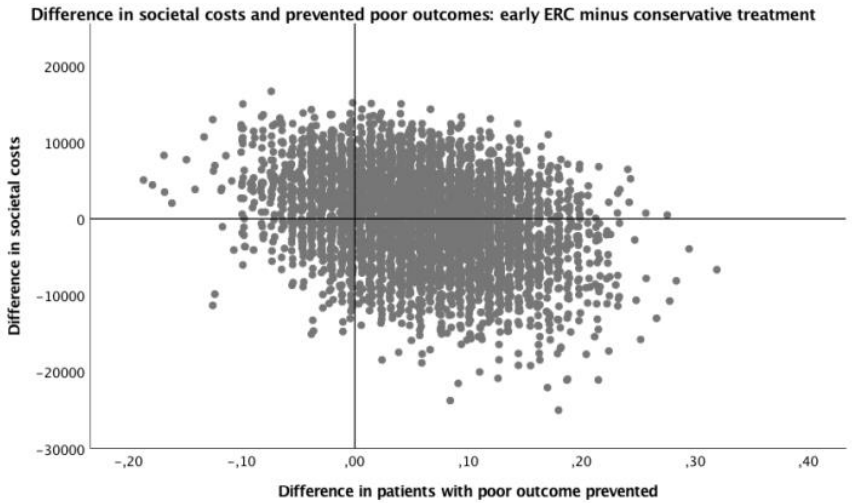
Table S4 Mean costs by treatment strategy

Table S4. Mean costs by treatment strategy

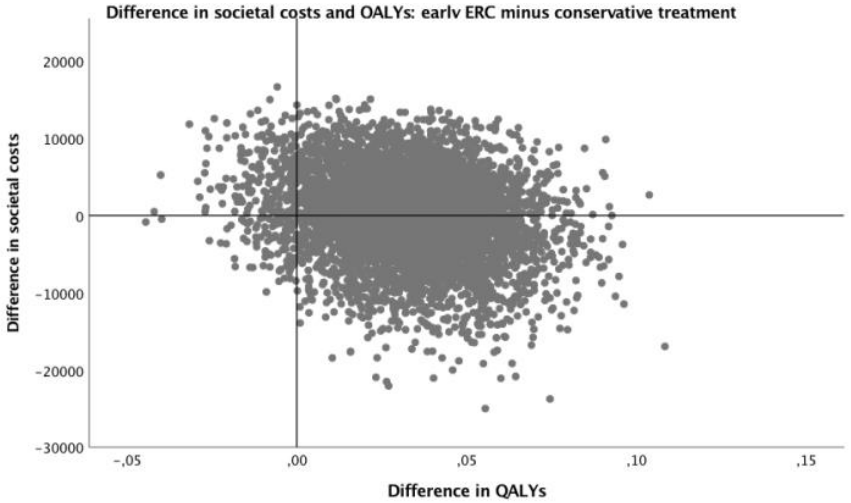
Mean Costs by treatment strategy	**Urgent ERCP with sphincterotomy** (N=117)	**Conservative treatment** (N=113)	**Difference ERCP minus conservative**
	Mean costs in € (BCa 95% CI)	**Mean costs in €** (BCa 95% CI)	**Mean costs in €** (BCa 95% CI; P-value)
Hospital care	**23436 (18222, 29353)**	**23675 (15958, 34457)**	**-239 (-13649, 10415; 0.971)**
ERCP with sphincterotomy	1210 (1126, 1298)	540 (366, 771)	670 (385, 883; <0.001)
Other procedures	5011 (4229, 5890)	5242 (4331, 6367)	-231 (-1794, 1114; 0.734)
Inpatient stay	16525 (11977, 21782)	17219 (10411, 26552)	-694 (-12905, 8954; 0.898)
Outpatient treatment	690 (618, 761)	674 (606, 745)	16 (-92, 117; 0.776)
Out-of-hospital care	**156 (112, 211)**	**119 (77, 178)**	**37 (-58, 120; 0.406)**
General practitioner	73 (59, 88)	58 (47, 70)	15 (-5, 36; 0.146)
Physiotherapist	83 (45, 131)	61 (24, 120)	22 (-72, 97; 0.608)
Formal home care	**155 (59, 278)**	**64 (22, 116)**	**91 (-12, 228; 0.178)**
Alpha help	52 (10, 107)	14 (0, 31)	38 (-8, 95; 0.215)
Family support	103 (24, 202)	50 (15, 93)	53 (-40, 162; 0.382)
Informal home care	**848 (497, 1307)**	**708 (415, 1056)**	**140 (-371, 685; 0.615)**
Family members	742 (393, 1209)	585 (325, 908)	157 (-338, 683; 0.544)
Others volunteers	66 (30, 107)	60 (17, 106)	5 (-68, 77; 0.876)
Paid private help	40 (19, 63)	62 (19, 114)	-22 (-93, 36; 0.504)
Travel costs	**33 (27, 40)**	**29 (23, 35)**	**4 (-5, 14; 0.387)**
Health care costs	***23746 (18713, 29359)***	***23859 (16340, 33550)***	***-112 (-13292, 10622; 0.987)***
Out-of-pocket expenses	***881 (524, 1324)***	***736 (456, 1079)***	***144 (-356, 681; 0.612)***
Societal costs	***24627 (19547, 30183)***	***24595 (17003, 34308)***	***32 (-13030, 10845; 0.994)***

Figure S2 Cost-effectiveness planes for incremental costs by incremental health effects

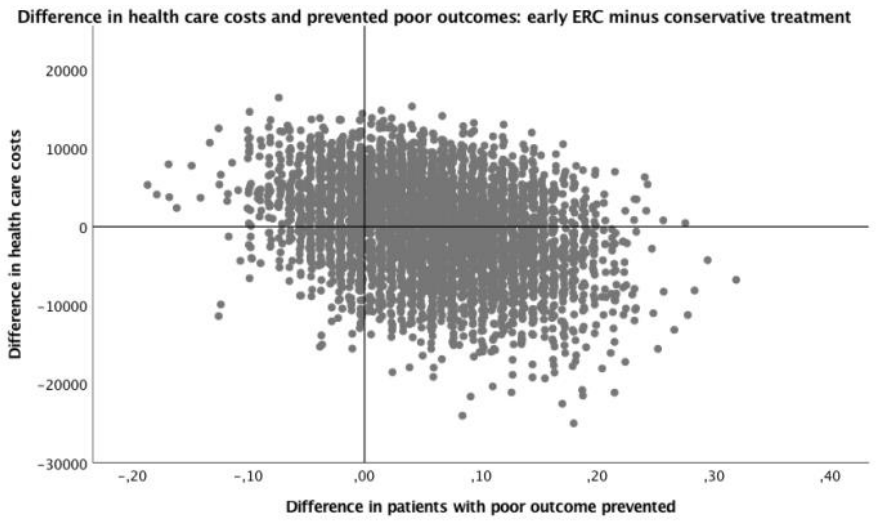
Figures S2a-d. Cost-effectiveness planes for incremental costs by incremental health effects

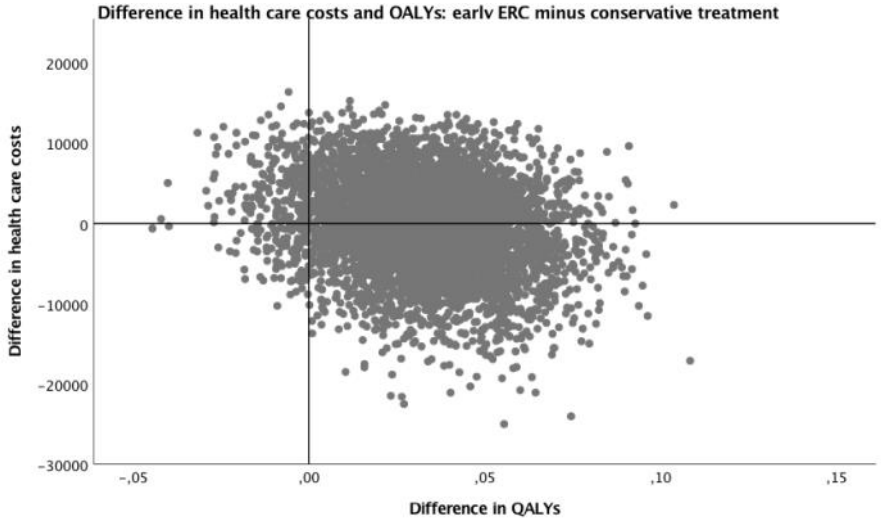


a. Extra societal costs per prevented poor outcome



b. Extra societal costs per additional QALY



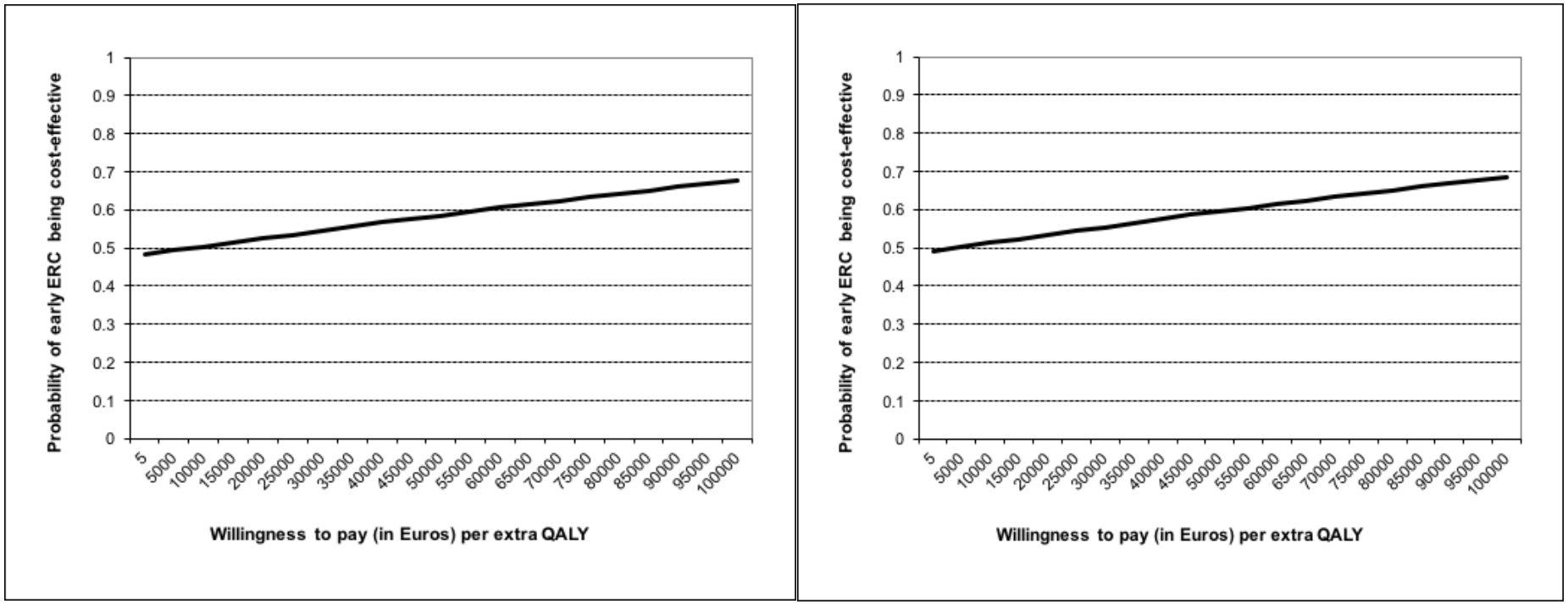


c. Extra health care costs per prevented poor outcome ***d. Extra health care costs per additional QALY***

From a societal perspective, urgent ERCP with sphincterotomy costs €533 per additional patient with a poor outcome prevented and costs only €972 per additional QALY. From a health care perspective urgent ERCP even dominates conservative treatment, being €1935 cost saving per patient with a poor outcome prevented and €3402 cost saving per additional QALY. These figures show the cost-effectiveness planes for incremental costs per patient with poor outcome prevented or per additional QALY from a societal perspective (S2a respectively S2b) and from a health care perspective excluding the out-of-pocket expenses (S2c respectively S2d). The figures demonstrate the uncertainty surrounding the point-estimated data. In all figures, the upper right quadrant reflects bootstrap results with extra costs and extra health gains (questionable), the upper left extra costs and extra health losses, the lower left costs savings and extra health losses, and the lower right costs savings and extra health gains. Urgent ERCP with sphincterotomy is cost saving (lower quadrants) from a societal perspective S2a and S2b) in 48.2% and from a health care perspective (S2c and S2d) in 49.1% bootstrap simulations; it is also more effective (quadrants on the right) in preventing patients having a poor outcome (S2a and S2c) in 81% and in generating QALYs (S2b and S2d)

in 94.1% bootstrap simulations. In at least 42.2% to 43% bootstrap simulations urgent ERCP is cost saving and more effective (lower right quadrant) than conservative treatment in preventing patients with a poor outcome, while conservative treatment is cost saving and more effective in at least 12.9% to 13% bootstrap simulations. With regard to QALYs, urgent ERCP is cost saving and more effective in 46.4% to 47.2% bootstrap simulations, and more expensive and less effective (upper left quadrant) in only 3.9% to 4.1% bootstrap simulations.

Figure S3 Cost-effectiveness acceptability curves for urgent ERCP versus conservative treatment



a. Societal perspective ***b. Health care perspective***

Figures S3 a-b show the cost-effectiveness acceptability curves from a societal, respectively health care perspective, expliciting the probability of urgent ERCP with sphincterotomy being efficient for willingness-to-pay values up to €100,000 euro per QALY. The probability of urgent ERCP being cost-effective ranges from 0.48 to 0.68 from the societal and from 0.49 to 0.69 from the health care perspective, depending on the societal willingness to pay per QALY. Considering that the target population in this trial encompassed acute pancreatitis patients with a predicted severe disease course if left untreated, an acceptable willingness-to-pay value would lie between €50,000 and €80,000 per QALY, where the probability would be about 0.59 to 0.65.

(Serious) Adverse events

						ERCP		Conservative		Total	
						Number	%	Number	%	Number	%
SAE's		**Patients (181-232)**	**Patients (121-180)**	**Patients (61-120)**	**Patients (1-60)**						
Safety Parameters	Death		AP128, AP132, AP137, AP143, AP150	AP065, AP80, AP081, AP092, AP107, AP110, AP111, AP113	AP007, AP036, AP054, AP044, AP059	8	9%	10	11%	18	10%
	ICU Admission		AP132, AP133, AP140, AP143, AP148, AP150, AP157, AP163, AP167, AP170, AP175	AP067, AP081, AP088, AP092, AP103, AP107, AP110, AP112, AP114, AP119	AP002, AP015, AP019, AP027, AP030, AP031, AP033, AP036, AP041, AP043, AP046	19	21%	13	14%	32	18%
Complication ERCP	Bleeding	AP187	AP139	AP061, AP069, AP073,AP074		4	4%	1	1%	5	3%
	Perforation		AP150, AP160, AP172, AP176	AP092		2	2%	3	3%	5	3%
	Respiratory insufficiency during ERC		AP134	AP092	AP054	3	3%	0	0%	3	2%
Other complications	Bacteremia	AP187, AP194, AP198, AP206, AP215, AP221, AP227	AP124, AP132, AP140, AP143, AP147, AP150, AP156, AP160, AP163, AP171, AP175, AP176	AP078, AP079, AP081, AP084, AP087, AP088, AP092, AP094, AP100, AP102, AP107, AP110, AP113, AP116, AP117, AP119	AP002, AP008, AP015, AP019, AP022, AP028, AP030, AP033, AP038, AP051, AP058, AP060	18	20%	22	24%	40	22%
	Positive urinary culture	AP198, AP206, AP209, AP216, AP227, AP230	AP074, AP119, AP128, AP132, AP133, AP135, AP140, AP152, AP156, AP157, AP163, AP168, AP169	AP065, AP069, AP074, AP078, AP088, AP094, AP101, AP113, AP114	AP016, AP022, AP026, AP048, AP051, AP058	12	13%	16	18%	28	16%
	Pneumonia	AP185, AP216, AP225, AP230	AP122, AP127, AP134, AP140, AP143, AP144, AP150, AP156,	AP076, AP080, AP088, AP092, AP103, AP107, AP112, AP113, AP114	AP002, AP046, AP045, AP054	14	16%	11	12%	25	14%

			AP157, AP160, AP166								
	Atrial fibrillation / arrythmia (new)	AP198, AP215, AP229	AP128, AP130, AP137, AP138, AP140, AP143	AP080, AP081, AP088, AP091, AP096, AP101, AP103, AP106, AP108, AP110, AP112, AP113, AP114	AP001, AP007, AP031AP041, AP043	14	16%	10	11%	24	13%
	Pancreasinsufficiency	AP184, AP223	AP096, AP116, AP133, AP134, AP138, AP140, AP149, AP162	AP064, AP065, AP072, AP073, AP080, AP082, AP083, AP094	AP001, AP010, AP024, AP021, AP026, AP030, AP045	14	16%	8	9%	22	12%
	Renal insufficiency	AP195, AP218	AP140, AP147, AP150, AP175	AP065, AP085, AP092, AP095, AP099, AP100, AP101, AP109, AP110, AP112, AP114, AP117	AP030, AP054, AP058	10	11%	9	10%	19	11%
	Peripancreatic collection		AP152, AP159, AP166, AP169, AP170, AP175	AP071, AP079, AP088, AP094, AP101, AP112, AP119	AP004, AP010, AP028, AP032 AP049, AP045	10	11%	9	10%	19	11%
	Respiratoire insufficiency	AP213, AP215	AP137, AP140, AP150, AP163, AP167	AP080, AP081, AP088, AP103, AP107, AP110, AP114, AP119	AP002, AP030, AP036, AP051, AP059	11	12%	7	8%	18	10%
	Pancreatic necrosis	AP181, AP184, AP186, AP209, AP227	AP133, AP134, AP166, AP167, AP173	AP092, AP094, AP109, AP110, AP112, AP114, AP115	AP026, AP055, AP06	8	9%	6	7%	14	8%
	Heart failure / decompensatio cordis	AP207, AP209, AP215	AP139, AP156, AP167	AP075, AP076, AP086, AP091, AP092, AP094, AP103, AP106, AP108, AP114		7	8%	6	7%	13	7%
	Cholangitis requiring ERCP	AP194, AP198, AP224	AP169, AP177	AP087, AP102	AP002, AP003, AP012, AP027, AP041, AP043, AP044, AP058	1	1%	11	12%	12	7%
	Ileus/ gastroparesis	AP213, AP225, AP230	AP119, AP125, AP134, AP167	AP065, AP081,AP096, AP101, AP103, AP107, AP119	AP060	10	11%	2	2%	12	7%

	Conversion laparoscopic to open cholecystectomy		AP127, AP152, AP160	AP093, AP103, AP104	AP006, AP011, AP031, AP042, AP058	8	9%	3	3%	11	6%
	Delirium	AP221	AP128, AP135, AP140, AP156, AP167	AP067, AP081, AP088, AP101, AP113, AP114		6	7%	5	6%	11	6%
	Hypopotassemia/Hyperpotassemia	AP194, AP198, AP213, AP229, AP230	AP122, AP125, AP131, AP134, AP135, AP143, AP152, AP164, AP167		AP053	6	7%	4	4%	10	6%
	Infected peripancreatische collection (with or without intervention)	AP184, AP186, AP193, AP215, AP216, AP225, AP230	AP128, AP132, AP138, AP140, AP143, AP150, AP163		AP031, AP038	5	6%	4	4%	9	5%
	Cholecystitis requiring percutaneous drainage	AP187, AP195, AP199	AP079, AP144	AP067, AP079, AP081, AP087	AP022, AP033	5	6%	3	3%	8	4%
	Cholecysitis requiring cholecystectomy	AP190, AP200, AP221	AP148, AP160	AP093	AP013, AP031, AP032, AP042	7	8%	0	0%	7	4%
	Recurrent pancreatitis	AP181, AP189, AP191, AP200, AP211	AP116, AP138, AP169	AP068	AP032, AP040, AP053	1	1%	6	7%	7	4%
	Myocardial infarction		AP069, AP140, AP150	AP067, AP088, AP096, AP107		4	4%	3	3%	7	4%
	Necrotising pancreatitis requiring drainage			AP088, AP119	AP002, AP019, AP031, AP044	3	3%	3	3%	6	3%
	Gout	AP199	AP125	AP095, AP101, AP116	AP016, AP022	3	3%	3	3%	6	3%
	(Re-)ERCP	AP191 , AP195, AP199, AP202, AP210, AP220, AP226, AP230	AP140, AP142, AP149, AP153, AP160, AP177			4	4%	2	2%	6	3%
	V. Porta trombosis/ V. Lienalis trombosis/VMS trombosis	AP181	AP133, AP150		AP008, AP030, AP045	3	3%	2	2%	5	3%
	Positive bile culture		AP079, AP157	AP067, AP103, AP110		4	4%	1	1%	5	3%
	Postoperative woundinfection/ infected hematoma	AP211	AP119, AP127, AP157	AP103	AP040	4	4%	1	1%	5	3%
	Readmission abdominal pain without known cause (e.c.i.)	AP181, AP212	AP144, AP168, AP170	AP085, AP095		4	4%	1	1%	5	3%
	Melena		AP074	AP074, AP087, AP092		1	1%	3	3%	4	2%
	Galbladderdrain after unsuccesfull ERCP		AP140, AP150	AP110	AP044	1	1%	3	3%	4	2%

	Symptomatic gallstone disease	AP188, AP189, AP199, AP210, AP226, AP230	AP069, AP091		AP043, AP049	3	3%	1	1%	4	2%
	Resudial in urinary bladder requiring catheter	AP205, AP224	AP061, AP074, AP168	AP116		2	2%	2	2%	4	2%
	Fever e.c.i. requiring antibiotics		AP122, AP123, AP139, AP155			3	3%	1	1%	4	2%
	Hemodynamic instability		AP133, AP137, AP140, AP150			3	3%	1	1%	4	2%
	Sepsis		AP140, AP143, AP156, AP157			3	3%	1	1%	4	2%
	Gastroenteritis				AP002, AP018, AP060	1	1%	2	2%	3	2%
	Fever, possibly cholangitis requiring antibiotics			AP083, AP084, AP098		1	1%	2	2%	3	2%
	Cholecystitis requiring antibiotics		AP169		AP004, AP018	2	2%	1	1%	3	2%
	Decubitus		AP157	AP088	AP030	1	1%	2	2%	3	2%
	ESBL+		AP145	AP067, AP103		3	3%	0	0%	3	2%
	Critical illness neuropathy		AP140	AP088, AP114		2	2%	1	1%	3	2%
	Clostridium infection	AP193	AP156, AP163		AP030	1	1%	2	2%	3	2%
	Orale candidiasis	AP185, AP216	AP133, AP160	AP065		2	2%	1	1%	3	2%
	Hypofosfatemia/Hypocalciemia/ other electrolyte disorder		AP122, AP156, AP167			2	2%	1	1%	3	2%
	Epileptic insult		AP127, AP128, AP133			2	2%	1	1%	3	2%
	Multiorganfailure	AP186, AP216	AP132, AP143, AP150			1	1%	2	2%	3	2%
	Poor regulated diabetes		AP133, AP141, AP157			2	2%	1	1%	3	2%
	Necrotising pancreatitis requiring drainage and necrosectomy				AP030, AP042	1	1%	1	1%	2	1%
	Bile duct injuring	AP192		AP103	AP003	1	1%	1	1%	2	1%
	Drug rash			AP092	AP035	1	1%	1	1%	2	1%
	CVA			AP088	AP044	0	0%	2	2%	2	1%
	Hypertension	AP206		AP063, AP092		2	2%	0	0%	2	1%
	ERCP for removal of PD stent		AP142		AP053	0	0%	2	2%	2	1%
	Laparotomy / percutaneous drainage for bile duct injury		AP157	AP103		2	2%	0	0%	2	1%
	Fistul bile duct- laparotomy wound / small intestine		AP157	AP103		2	2%	0	0%	2	1%

	Papiladenoma requiring biopsy		AP148	AP111		1	1%	1	1%	2	1%
	Postoperative pain requiring readmission		AP124, AP160			1	1%	1	1%	2	1%
	Bleeding pancreas		AP128, AP133			1	1%	1	1%	2	1%
	Obstipation	AP220	AP136, AP166			1	1%	1	1%	2	1%
	Retained CBD stone		AP142, AP172			0	0%	2	2%	2	1%
	Pleural effusion		AP152, AP160			1	1%	1	1%	2	1%
	Hernia cicatricalis				AP024	1	1%	0	0%	1	1%
	Bleeding aneurysma a. lienalis requiring coiling				AP030	0	0%	1	1%	1	1%
	Bleeding a. pancreaticoduodenale requiring coiling				AP008	1	1%	0	0%	1	1%
	Bloeding a. gastroomentalis requiring coiling			AP088		0	0%	1	1%	1	1%
	V. Jugularis trombosis				AP030	0	0%	1	1%	1	1%
	Pseudoshub (Multiple Sclerosis)				AP021	1	1%	0	0%	1	1%
	Skin rash				AP026	0	0%	1	1%	1	1%
	Pyleonefritis				AP039	0	0%	1	1%	1	1%
	Appendicitis acuta				AP041	0	0%	1	1%	1	1%
	Aneurysm a. ileaca interna				AP058	0	0%	1	1%	1	1%
	Drainage biloma and stent CBD				AP049	0	0%	1	1%	1	1%
	Immune thrombocytopenic purpura				AP037	0	0%	1	1%	1	1%
	Vaginal candidiasis				AP030	0	0%	1	1%	1	1%
	Recurrent hipluxation				AP045	1	1%	0	0%	1	1%
	Bleeding after percutaneous drainage			AP087		0	0%	1	1%	1	1%
	Erysipelas requiring antibiotics			AP088		0	0%	1	1%	1	1%
	Abdominal compartiment syndrome	AP186		AP088		0	0%	1	1%	1	1%
	Fall out of bed			AP092		0	0%	1	1%	1	1%
	Anemia requiring transfusion			AP094		1	1%	0	0%	1	1%
I	Influenza infection			AP094		1	1%	0	0%	1	1%
	Norovirus infection			AP101		1	1%	0	0%	1	1%

	Jejunumperforation requiring laparotomy			AP103		1	1%	0	0%	1	1%
	Gallbladdercarcinoma			AP103		1	1%	0	0%	1	1%
	Subtotale= cholecystectomy			AP104		1	1%	0	0%	1	1%
	Stomaprolaps			AP105		0	0%	1	1%	1	1%
	Gastric perforation			AP107		0	0%	1	1%	1	1%
	Fausse route during CAD placement			AP110		0	0%	1	1%	1	1%
	Recurrent T-cel lymfoma/NHL	AP211		AP111		0	0%	1	1%	1	1%
	Glomerulonefritis			AP112		0	0%	1	1%	1	1%
	Cholecystitis with liver abces		AP079			1	1%	0	0%	1	1%
	Hypotension		AP091			1	1%	0	0%	1	1%
	Movement disorder e.c.i.		AP123			0	0%	1	1%	1	1%
	Meningitis		AP127			1	1%	0	0%	1	1%
	Dermatomycosis		AP128			0	0%	1	1%	1	1%
	Pericardial effusion		AP129			0	0%	1	1%	1	1%
	Restlessness requiring intubation and sedation		AP133			1	1%	0	0%	1	1%
	Spleen infarction		AP138			0	0%	1	1%	1	1%
	Kidne infarction		AP138			0	0%	1	1%	1	1%
	Pancreascarcinoma		AP141			0	0%	1	1%	1	1%
	Subfrenic abces		AP141			0	0%	1	1%	1	1%
	Bleeding a. gastroduodenale requiring coiling		AP143			1	1%	0	0%	1	1%
	Bile peritonitis		AP144			0	0%	1	1%	1	1%
	Rectushematoma		AP144			0	0%	1	1%	1	1%
	Papil Vater carcinoma		AP148			1	1%	0	0%	1	1%
	Pulmonary cancer		AP148			1	1%	0	0%	1	1%
	Bowel ischaemie		AP150			0	0%	1	1%	1	1%
	Anastomotic leakage after bowel dissecition		AP150			0	0%	1	1%	1	1%
	(Multiple) intraabdominal abces	AP218	AP157			1	1%	0	0%	1	1%
	Rectalcarcinoma		AP159			1	1%	0	0%	1	1%
	Impending obstructcion rectal cancer		AP159			1	1%	0	0%	1	1%

	Opioid intoxication		AP160			1	1%	0	0%	1	1%
	Hematuria requiring readmission		AP176			0	0%	1	1%	1	1%
	Contrastallergy	AP182				1	1%	0	0%	1	1%
	Hyperthyreoidy	AP191				0	0%	1	1%	1	1%
	Endometrial cancer	AP207				1	1%	0	0%	1	1%
	Malnutrition	AP213				1	1%	0	0%	1	1%
	Pumonary embolism	AP215				1	1%	0	0%	1	1%
	Chylusleakage (abdominal/thoracal)	AP215				1	1%	0	0%	1	1%
	Infected ascites	AP215				1	1%	0	0%	1	1%
	Oesophagisbleeding	AP216				1	1%	0	0%	1	1%
	Collaps due to hypoglycaemia	AP229				1	1%	0	0%	1	1%
	Chronic pancreatitis	AP200				1	1%	0	0%	1	1%
Total number SAE's						286		238		524	
Number of patients with 1 or more SAE's in ERCP-arm		AP182, AP184, AP185, AP186, AP187, AP193, AP198, AP199, AP205, AP207, AP213, AP215, AP216, AP218, AP220, AP221, AP225, AP229	AP122, AP125, AP127, AP133, AP134, AP136, AP137, AP139, AP140, AP143, AP145, AP147, AP149, AP155, AP157, AP159, AP160, AP161, AP163, AP164, AP167, AP168, AP170	AP061, AP063, AP067, AP069, AP072, AP073, AP079, AP080, AP081, AP083, AP085, AP091, AP092, AP093, AP095, AP096, AP099, AP103, AP104, AP114, AP115, AP117, AP119	AP001, AP006, AP007, AP008, AP010, AP013, AP018, AP019, AP021, AP024, AP028, AP031, AP032, AP033, AP036, AP038, AP042, AP043, AP045, AP046, AP051, AP054, AP060					87 / 118 =	74%
Number of patients with 1 or more SAE's in conservative-arm		AP181, AP188, AP189, AP190, AP191, AP192, AP194, AP195, AP200, AP202, AP206, AP209, AP210, AP211, AP212, AP223, AP224, AP226, AP227, AP230	AP123, AP124, AP128, AP129, AP130, AP131, AP132, AP135, AP138, AP141, AP142, AP144, AP148, AP150, AP152, AP156, AP162, AP166, AP169, AP171, AP172, AP173, AP175, AP176, AP177	AP065, AP068, AP071, AP074, AP075, AP076, AP078, AP082, AP084, AP086, AP087, AP088, AP098, AP100, AP106, AP107, AP108, AP109, AP111, AP112, AP113, AP116	AP002, AP003, AP004, AP003, AP011, AP012, AP015, AP016, AP022, AP026, AP027, AP030, AP035, AP037, AP039, AP040, AP041, AP044, AP048, AP049, AP053, AP055, AP058, AP059					91 / 114 =	80%

Original and Final Trial Protocol; Overview of Amendments made

Original trial protocol d.d. 10-4-2012 (see separate file)

Trial protocol submitted and approved by ethical committee d.d. 3-11-2012 (see separate file)

First amendment d.d. 11-4-2014 (see separate file)

Second amendment d.d. 17-2-2015 (see separate file)

Date	Amendments made
April 2014	*Administrative* 1. Addition of another 4 participating hospitals, and removal of 1 hospital. 2. Changes in personal data (CVs etc) of local investigators and addition of documents for approval in participating hospitals 3. New location of the datacenter of the Dutch Pancreatitis Study Group (from Radboud University Medical Center, Nijmegen, to St. Antonius Hospital, Nieuwegein. *Substantive* 1. Page 6. Removal of the word "conversion" from the trial protocol to avoid confusion. "Conversion" suggests that patients switch from treatment arm 2. Page 9. Correct definition of pancreatic necrosis. Previously "necrotising pancreatitis" was mentioned, which included extrapancreatic necrosis. The sample size calculation of the APEC trial is based on pancreatic necrosis. 3. Page 27: Addition and clarification of a trial monitoringplan. 4. Page 33: Concerning data assessed by the Data Safety Monitoring Commmittee: removal of the prequisite that patients assessed should have fulfilled 30 days of follow-up after discharge. Without this restriction, all available patient data known can be evaluated by the DSMC. 5. Page 41: Removal of paragraph concerning informed consent by representatives, in case of severe illness. In the APEC trial all patients had to give informed consent themselves. 6. Page 43: According to the legal requirements we increased the period that source documents should be kept, from 10 to 15 years.

	7. Page 48: Definition of organ failure are adjusted according to the revised Atlanta Classification. 8. Page 51: Clarified the Dutch translation of the APACHE-II definition 9. Page 53 to 56: Additional information regarding the members of the Expert panel, the Data Safety Monitoring Committee, Adjudication Committee and Steering Committee.
Februari 2015	1. Addition of side-study to the APEC trial that investigates predictors of severity in acute pancreaittis 2. Change of local investigators. 3. Concerning secondary research questions and parameters: whether urgent ERCP reduces cholangitis during initial admission.

Overview of Amendments made in Statistical Analysis Plan

Date	Amendments made
Nov 2012	Please see "track change" version for detailed changes. In summary we provided additional information regarding: 1. Intention-to-treat and per-protocol population 2. The computer program for performing the analysis 3. Data handling will be saved in a synthax/ program file 4. Baseline covariates 5. Specific analyses for the components of the primary end point 6. Explanatory analysis 7. Secondary efficacy measures, including time-to-event analyses 8. Interim-analysis: specification to performed interim analysis when 50% of randomized patients is *discharged* from the hospital. 9. Definitions of (serious) adverse events
March 2016	1. Addition of "introduction", "objective" and "study design" paragraph 2. We added the published trial protocol as reference

Statistical Analysis Plan

INTRODUCTION

This statistical analysis plan relates to the trial entitled: ***A****cute biliary* ***P****ancreatitis: urgent* ***E****RCP with sphincterotomy versus* ***C****onservative treatment: the - APEC – trial*. For more information about the clinical trial we refer to the published trial-protocol.[9]

The analysis will be performed by the department of Epidemiology & Biostatistics, Erasmus MC by the biostatistician, in collaboration with the study coordinator. The sequential safety analysis on death and interim-analysis will be performed by the independent biostatistician from the Epidemiology & Biostatistics department of het University Medical Center Utrecht. Economical analyses are performed by the Health Technology Assessment-expert of the department Epidemiology & Biostatistics of the Academic Medical Center in Amsterdam.

The results achieved will be used for scientific publications.

TRIAL OBJECTIVE

The APEC trial is designed to investigate whether urgent ERCP with sphincterotomy compared with conservative treatment improves outcome in patients with biliary pancreatitis without cholangitis who are at high risk for complications.

STUDY DESIGN

The APEC trial is a randomised controlled, parallel group, superiority, multicentre trial. Patients with acute pancreatitis will be assessed for study eligibility within 24 hours after presentation to the emergency department. Patients with biliary pancreatitis without cholangitis and at high risk of developing severe disease are eligible for randomization. Patients are randomised to urgent ERCP with sphincterotomy or to conservative treatment. Blinding of the patients and physicians for either treatment (ERCP or conservative treatment) is unfeasible. The trial will be conducted in 26 hospitals of the Dutch Pancreatitis Study Group. Patients are randomised to urgent ERCP with sphincterotomy or to conservative treatment (1:1 ratio). At randomization, patients are stratified according to the presence of cholestasis and for region of the hospital. Urgent ERCP with sphincterotomy is performed within 72 hours after symptom onset and within 24 hours of hospital admission. Patients in the conservative group are managed according to the conservative supportive treatment regimen for patients with acute

biliary pancreatitis. A rescue ERCP is performed when a patient develops cholangitis. Retained bile duct stones are removed during an elective ERCP when the patient is recovered from the initial pancreatitis episode.

ENDPOINTS

The primary endpoint is a composite of death or severe complications occurring within 180 days after randomization (that is, the composite endpoint can only occur once per patient). Severe complications are defined as persistent organ failure, pancreatic necrosis, bacteremia, cholangitis, pneumonia, and pancreatic endocrine or exocrine insufficiency.

The secondary endpoints are as follows:

1. "Per protocol" analysis of the primary endpoint
2. "As treated" analysis of the primary endpoint
3. Individual components of the primary endpoint
4. Multivariable analysis of the primary endpoint in case of significant differences in baseline variables
5. Infected necrotising pancreatitis
6. Need for new intensive care unit admission
7. Length of stay at intensive care unit
8. ERCP-related complications
9. Cholangitis during admission
10. Number of endoscopic, radiological, and operative (re-)interventions
11. Readmission for biliary events (recurrent acute biliary pancreatitis, cholecystitis, biliary colics, or cholangitis)
12. Difficulty of cholecystectomy (as scored by Visual Analog Scale 1 to 10)
13. Quality of life (Short Form-36 and EQ5D-5 L) including quality adjusted life years (QALY)
14. Direct medical costs and direct and indirect nonmedical costs

SEQUENCE OF PLANNED ANALYSIS

The final data, checked for plausibility and validity, are checked by the study coordinator. Only after this, the final stastistical analysis is performed by the biostatistician. All statistical analysis are performed via syntax or program files.

SAMPLE SIZE CONSIDERATIONS

At randomization, patients are stratified according to the presence of cholestasis and for region of the hospital.

The sample size calculation is based on a recent Dutch multicentre observational study of patients with biliary pancreatitis at high risk for complications.[10] The primary endpoint occurred in 32 % of the patients in which ERCP was performed compared with 46 % of the patients who were treated conservatively. Taking into account that ERCP was not always performed within 24 hours and that sphincterotomy was not routinely performed, a correction factor of 2 % for both percentages is added to both incidence rates. The APEC trial is a superiority trial in which the sample size calculation is based on the assumption that urgent ERCP with sphincterotomy reduces the incidence of the primary endpoint by 18 % (48 % to 30 %). With a power of 80 %, a two-sided significance level of 5 % and a 1 % drop-out rate, a total of 232 patients are required to be included in the study (http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html, accessed 20 July 2015)).

ANALYSIS POPULATION

All randomised subjects will be evaluated for primary and secondary endpoints at 180 days after randomization.

After 232 patients have completed their 6 months of follow-up, raw data regarding potential endpoints will be presented to an adjudication committee blinded to the treatment allocation to determine whether the endpoints meet the protocol-specified criteria. The study coordinator will blind the patient reports for treatment allocation. Each member of the committee will individually assess the potential endpoints. In case of dissenting opinions, a consensus meeting will follow. Only after consensus has been reached on each individual endpoint for each individual patient will a final analysis be

performed by an independent statistician, unblinded for treatment allocation.

The primary analysis will be based on intention to treat principles. For exploratory reasons also a per-protocol analysis will be performed.

- Intention-to-treat population: comprises all patients included in the study who were randomised, regardless with patients being analyzed according to original treatment allocation, regardless of whether the cannulation or sphincterotomy was successful.
- Per-protocol population: is the subset of randomised patients who were treated with the guidelines of the protocol.

A tabular listing of all patients excluded from the intention-to-treat populations will be provided together with the reasons for exclusion. For both intention-to-treat- and per-protocol population the protocol deviations, overall and by centre for each randomisation arm, will be listed.

INTERIM ANALYSIS

An interim-analysis will be performed when 116 patients (50%) have been randomised and discharged after their initial hospital admission. Raw data pertaining to potential endpoints will be presented to an adjudication committee blinded for treatment allocation to determine whether the endpoints meet the protocol-specified criteria. In case of dissenting opinions, a consensus meeting will follow. The interim-analysis will be performed by an independent statistician who reports to the DSMC. The DSMC will have unblinded access to all data when discussing the results of the interim-analysis and when reporting to the steering committee. The steering committee will decide upon continuation of the APEC trial. The Haybittle-Peto approach is used for beneficial effect, meaning that the trial will be ended using symmetric stopping boundaries at $P < 0.001$.[2,3] The trial will not be stopped for futility.

GENERAL CONSIDERATIONS FOR DATA ANALYSIS

All analysis will be performed in SPSS for Windows or SAS System for Windows. All data handling and analysis will be saved in a syntax/program file. Results will be presented with all centres combined. A two-tailed p-value < 0.05 is considered statistically significant. No corrections for multiple tests are applied.

BASELINE COVARIATES

The following patient characteristics before randomization will be described: age, sex, body mass index, comorbidity, American Society of Anesthesiologists (ASA) score, duration of symptoms before randomization, duration of symptoms before ERCP, serum bilirubin levels, dilated common bile duct on ultrasound or computed tomography, presence of (multi) organ failure or systemic inflammatory

response syndrome (SIRS), Sequential Organ Failure Assessment (SOFA) scale, (ref) Multiple Organ Dysfunction Score (MODS),[4,5] predicted disease severity according to APACHE-II, modified Glasgow, blood urea nitrogen, and C-reactive protein. Data will be presented in percentages for categorical variables. Continuous data with a normal distribution will be presented as a mean with standard deviation and as median with interquartile range in case of skewed distribution.

MISSING DATA

Data on the primary and secondary endpoints that are missing will be categorized as no event. For other analyses, data will be considered missing at random.

PROTOCOL DEVIATIONS

For both intention-to-treat- and perprotocol population the protocol deviations, overall and by centre for each randomisation arm, will be listed.

EFFICACY ANALYSIS

PRIMARY EFFICACY MEASURE

The primary endpoint is a composite of death and severe complications occurring within 180 days after randomization. Severe complications are defined as the occurrence of persistent single organ failure, pancreatic necrosis, bacteremia, cholangitis, pneumonia, exocrine or endocrine pancreatic insufficiency.

- The percentage of patients that reach the primary endpoint will be compared between the two treatment groups using the Pearson's chi-squared test. Relative risk with 95% confidence interval will be presented.
- Analysis of the primary endpoint will also be presented adjusted for patients with versus without cholestasis at presentation (for this subgroup stratification at randomization is applied). Logistic regression models will be used as formal tests for interaction to assess whether treatment effects differ significantly between these subgroups.
- To gain further insight in factors predicting death and severe complications after ERCP, explanatory analysis of the effects of (essential) baseline covariates (and potential interactions) will be performed using logistic regression analysis.

SECONDARY EFFICACY MEASURES

- Individual components of the primary endpoint will be compared between treatment arms using the Pearson's chi-squared test. Relative risks with 95% confidence intervals will be presented. Additionally, they will be analyzed separately by the Kaplan Meier method censoring patients no longer at risk.
- Length of hospital stay, intensive care stay and number of endoscopic, radiological and operative (re-)interventions will be compared between treatment arms using the Mann-Whitney U test.

- The following secondary endpoints will be compared between treatment arms using the Pearson's chi-squared test. Additionally they will be analyzed by the Kaplan Meier method censoring patients no longer at risk.
    - Need for intensive care admission
    - ERCP related complications
    - Respiratory complications after randomization
- Readmission for biliary events (recurrent ABP, cholecystitis, biliary colics, cholangitis) will be compared between treatment arms using the Pearson's chisquared test. Additionally they will be analyzed separately the Kaplan Meier method censoring patients no longer at risk. Hospital discharged will be used as t=0. For the analysis length of hospital stay prior to discharge is studied as a covariate.
- Difficulty of cholecystectomy will be compared between treatment arms using the Mann-Whitney U.
- Economical evaluation: costs will be compared between treatment arms using samples t-tests.

ADDITIONAL ANALYSIS

Predefined subgroup analysis will be done according to the presence of cholestasis. Logistic regression models will be used to test whether treatment effects differ significantly between these subgroups. In addition to the comparison of secondary endpoints with the Pearson's chi-squared test or Mann-Whitney, secondary endpoints will be analyzed separately using Cox regression analysis censoring patients no longer at risk and categorizing missing data as no event. To evaluate differences in systemic inflammatory response after randomization, the APACHE-II, C-reactive protein levels, and presence of SIRS from randomization to day 7 will be calculated and compared between the treatment groups. To gain further insight into factors that are predictive of severe complications or death after ERCP, an exploratory analysis of the effects of (essential) baseline covariates (and potential interactions) will be performed using logistic regression analysis. The essential baseline covariates that will be studied are demographics, comorbidity, predicted severity prior to randomization, presence of organ failure prior to randomization, cholestasis, and duration of symptoms prior to randomization. In addition, the time between the start of symptoms and the ERCP will be studied.

The impact of differences in complications on the quality of life of pancreatitis patients will be assessed with the well-known and frequently applied generic quality of life questionnaire, the SF-36.[1] The SF-36 will be completed at 30, 90 and 180 days after randomization. The SF-36 data will be analyzed as repeated measures by linear mixed modeling.

In the economical analysis, a cost-effectivity and cost-utitlity analysis will be performed. Direct medical and nonmedical costs and indirect costs will be compared to assess costs per patient with poor outcome (death or severe complications). Validated questionnaires will be analyzed to assess differences in the quality of life and provide input to compare costs per quality-adjusted life year (QALY). Health utility scoring algorithms for the EQ5D-5 L health status profiles available from the literature, based on preferences in the general population using time trade-off elicitation techniques, will be used to derive a QALY estimate for each patient. This QALY will be calculated as the product sum of health utilities and the lengths of the periods between the successive measurements.[11,12]
At final analysis, the association between (serious) adverse events and the treatment arm with baseline essential covariates will be analyzed with Pearson's chi-squared tests or analysis of variance methods.

SAFETY ANALYSIS

An independent Data Safety Monitoring Committee (DSMC) has been appointed to assess protocol adherence, patient recruitment, and patient safety. All physicians who are involved in the trial are asked to report all adverse events to the coordinating investigator. Adverse events are reported using the online module (https:// www.toetsingonline.nl) of the Dutch Central Committee on Research involving human subjects. All adverse events are collected and reported unblinded to the
DSMC every time 60 patients are randomised, after randomization of the final patient, and at the end of follow-up of the final patient. In addition, a continuous sequential safety analysis on mortality is performed by the independent statistician to ensure the patient's safety throughout the trial. The DSMC discusses all adverse events and the progress of the trial and reports to the trial steering committee. A copy is sent to the ethical committee and all physicians who are involved with the study.

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References

1. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
2. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. The British journal of radiology 1971;44:793-7.
3. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomised clinical trials requiring prolonged observation of each patient. I. Introduction and design. British journal of cancer 1976;34:585-612.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
5. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Critical care medicine 1995;23:1638-52.
6. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc 1991;37:383-93.
7. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000;21:1502-13.
8. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.
9. Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomised controlled trial. Trials 2016;17:5.
10. van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicentre study. Ann Surg 2009;250:68-75.
11. M MV, K MV, S MAAE, de Wit GA, Prenger R, E AS. Dutch Tariff for the Five-Level Version of EQ-5D. Value Health 2016;19:343-52.
12. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PloS one 2017;12:e0187477.