Pancreatic **C**yst **F**ollow-up, an **I**nternational **C**ollaboration **PACYFIC study**

A prospective evaluation of pancreatic cyst surveillance, based on the European expert consensus statement on cystic tumours of the pancreas

Version 5, 31th of October 2018

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PROTOCOL TITLE Pancreatic Cyst Follow-up, an International Collaboration

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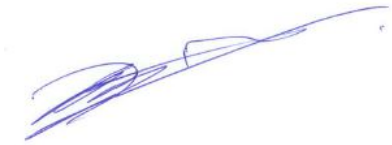
Sponsor or legal representative: **For non-commercial research,** **Head of Department:** Prof. Dr M.J. Bruno, Head of Department of Gastroenterology & Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands		**31-10-2018**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BD-IPMN	**Branched-Duct Intraductal Papillary Mucinous Neoplasm**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CT	**Computed Tomography**
CV	**Curriculum Vitae**
DPCG	**Dutch Pancreatic Cancer Group**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EUS	**Endoscopic Ultrasonography**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICMJE	**International Committee of Medical Journal Editors**
IPMN	**Intraductal Papillary Mucinous Neoplasm**
METC	**Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)**
MISCAN	**Micro-Simulation Screening Analysis**
MCA	**Mucinous Cystadenoma**
MD-IPMN	**Main-Duct Intraductal Papillary Mucinous Neoplasm**
MPD	**Main Pancreatic Duct**
MRCP	**Magnetic Resonance Cholangiopancreatography**
MRI	**Magnetic Resonance Imaging**
(S)AE	**(Serious) Adverse Event**
SCA	**Serous Cystadenoma**
SPN	**Solid Pseudopapillary Neoplasm**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or**

	investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UEG	**United European Gastroenterology**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Asymptomatic pancreatic cysts are a common finding in this time of elaborate imaging. The malignant potential of these cysts is probably small, but exact data regarding cancer risks are limited. Generally, an intensive surveillance strategy is chosen, driven out of fear to miss one of the deadliest cancers, and based on international recommendations. In 2013, a group of European experts formulated a consensus statement, recommending lifelong follow-up with Magnetic Resonance Imaging (MRI), every 6 to 12 months. This strategy may be justified for some individuals, to timely detect malignant progression, but in the majority of cases, cysts will never progress. Consequently, these patients are likely to undergo lifelong redundant (and costly) investigations.

Objectives: To establish the yield of pancreatic cyst surveillance, based on the recently published European evidence-based guidelines(1), and to identify possible alternative, more (cost) effective, surveillance strategies.

Study design: An international multicentre observational cohort study that will run for 10 years. The first analysis will take place after three years.

Study population: Patients with a pancreatic cyst - either newly diagnosed, previously diagnosed, or previously operated upon - that requires surveillance in the opinion of the treating physician.

Intervention: Cyst surveillance will be performed by the treating physician at the hospital of origin. Based on the recommendations of the EU guidelines(1), patients will be followed every 6 to 12 months by imaging studies (preferably Magnetic Resonance Imaging (MRI/MRCP), with endoscopic ultrasonography (EUS) as an alternative) and determination of serum CA 19.9 levels. Cyst management will remain in the hands of the treating physician. Both treating physicians and participating subjects will provide outcome data, by filling out (on-line) case record forms (CRF) and questionnaires. Blood and pancreatic juice are collected each follow-up or EUS, respectively.

Main study parameters/endpoints: Primary endpoints are: the number of patients that reach an indication for surgical cyst resection and the number of patients diagnosed with a malignant cyst (either high-grade dysplasia or carcinoma). Secondary endpoints are: 1. the outcome of patients with an indication for cyst resection; i.e. the number of operated patients, surgical procedures, morbidity, mortality, and cyst recurrence, 2. cyst evolution, in terms of development of symptoms, cyst growth, and other worrisome features, and 3. the perceived burden of surveillance on participants. Other study parameters are; 4. possible risk factors for malignancy, either patient or cyst related, and 5. to build a micro-simulation screening analysis (MISCAN) model, based on the outcome data of this study, in order to determine the optimal strategy for pancreatic cyst surveillance.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There will be no risks involved for patients participating in this study. The follow-up schedule is in accordance with current common practice, and based on recently published surveillance recommendations (2, 3). The only burden for participating patients may be providing four additional blood vials at each blood withdrawal, that is recommended by the guidelines, and filling out an online questionnaire at baseline and during follow-up. In the Erasmus University Medical Center pancreatic juice is collected during EUS, which prolongs the EUS procedure with 5-10 minutes. A potential benefit of study participation is a better compliance to the surveillance program.

1. INTRODUCTION AND RATIONALE

Incidental pancreatic cysts are prevalent, in particular in this day and age of cross-sectional imaging (4). The reported incidence depends on the applied imaging technique and the investigated setting. In CT series of symptomatic patients, the incidence varies from 1 to 3% (5). In healthy individuals undergoing a screening MRI, we found a pancreatic cyst in 2.4% (6). An autopsy series by Kimura even reported a prevalence rate of 24%(7).

These cysts form a heterogeneous group of non-neoplastic and neoplastic lesions, with variable pathologic features, clinical presentation, and outcome. Most cysts are (virtually) benign, such as Pseudocysts and Serous Cystadenomas (SCA), and, when asymptomatic, do not require treatment or follow-up. However, some neoplastic cysts have a malignant potential (Mucinous cysts and Intraductal Papillary Mucinous Neoplasms (IPMN)), and require follow-up or even a surgical resection (8, 9). Unfortunately, to distinguish these pancreatic cysts, especially the smaller ones, is often impossible(10).

A second problem in pancreatic cyst management is that data regarding the natural history and predictive factors for malignant degeneration are virtually lacking (3, 11). The literature is biased by highly selected patient series from tertiary referral centres. Sahani reported a 13% risk of malignancy in cysts smaller than 3 cm(3). In asymptomatic cysts, the reported prevalence of carcinoma varies between 1 and 3% (9). However, the malignant potential is likely to be much lower, considering the high prevalence of pancreatic cysts and the low incidence of malignant cystic neoplasms. Fitzgerald, for instance, reported a yearly incidence of malignant pancreatic cysts from a state-wide tumour registry in Michigan, USA, of 0.47/100.000(8). Given the 2.4% incidence of pancreatic cysts on screening MRI's, the calculated malignancy rate would be no more than 0.0002 per year (6).

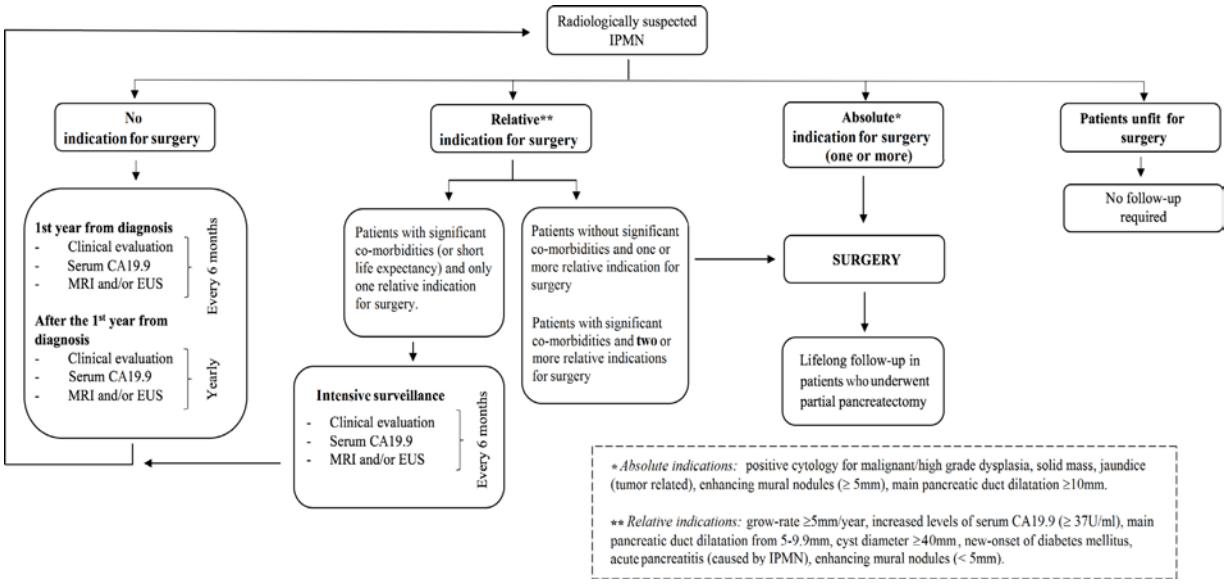
Because it is impossible to estimate the cancer risk of small pancreatic cysts, treating physicians face a difficult dilemma: to miss a pancreatic carcinoma, or to expose the majority of patients with a benign cystic lesion to redundant investigations, or even unnecessary surgery (with substantial morbidity and mortality). At present, an intensive surveillance strategy is generally chosen, driven out of fear for one of the deadliest cancers.

In 2012, a group of European experts (the European study group on cystic tumours of the pancreas) formulated a consensus statement regarding the management of pancreatic cystic neoplasms(2), which were updated into the 'European evidence-based guidelines on pancreatic cystic neoplasms' in 2018(12). These recommendations address the use of imaging techniques, criteria for resection, and a schedule for cyst surveillance. For small,

undifferentiated cysts and side-branch IPMN's, without signs of malignancy, they recommend an intensive follow-up strategy, with lifelong surveillance by MRI and determination of serum CA19.9, every 6 to 12 months. Despite the absence of solid evidence, this surveillance advice is widely implemented in clinical practice. Therefore, these recommendations require prompt validation by a prospective cohort study.

Figure 1 Graphical outline of recommended surveillance protocol and the indications for surgery, based on the 2018 European evidence-based guidelines(12)

EUS: endoscopic ultrasound; IPMN: intra-ductal papillary mucinous neoplasm.



Generally, for a surveillance program to be implemented, a yield of 0.2% is required (identifying 5 cases per 1000 subjects followed). To evaluate surveillance strategies, a MIcro-simulation SCreening ANalysis (MISCAN) model may be used (13-15). This widely established mathematical model was developed by the department of Public Health of the Erasmus Medical Center of Rotterdam in 1987. Based on real outcome data from different sources, the model generates a large fictitious population. Not only can it evaluate the subjected screening strategy, but it can also predict the outcome of alternative strategies, in order to optimize future screening. This model was also used to establish the value of colorectal cancer screening in the Netherlands (16).

2. OBJECTIVES

Primary objective

To establish the yield of regular pancreatic cyst surveillance, based on the European evidence-based guidelines on pancreatic cystic neoplasms, in terms of identified patients that require cyst resection, diagnosed malignancies, cyst evolution, and the perceived burden for participants.

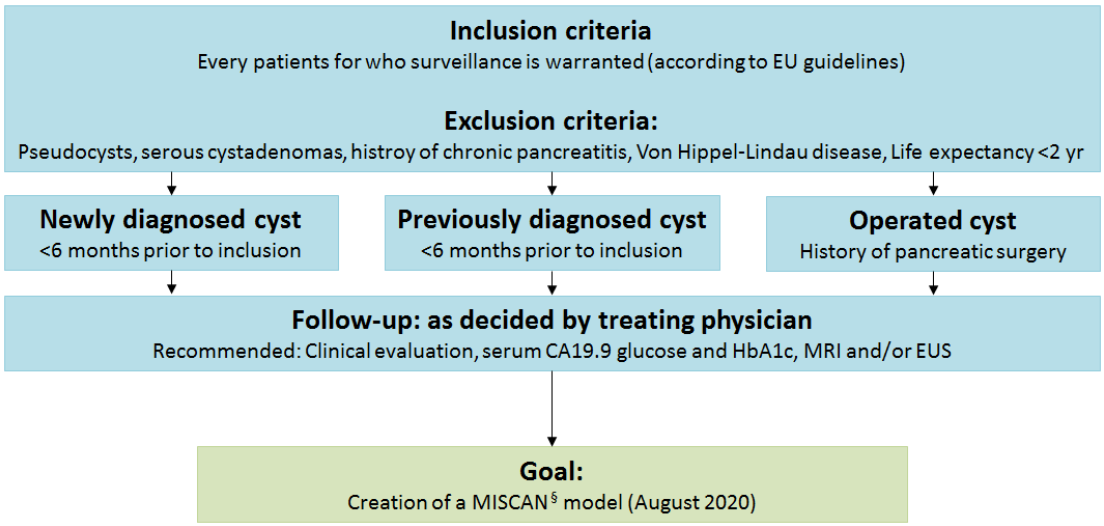
Secondary objective

To identify more (cost) effective surveillance strategies, using acquired information on the natural course of the disease, identified risk factors for malignancy, and calculations from a MISCAN model for cyst surveillance.

3. STUDY DESIGN

The study is designed as a prospective international multicenter cohort study, which will be coordinated by the department of Gastroenterology and Hepatology of the Erasmus University Medical Center of Rotterdam, the Netherlands. The study will run for ten years. Patients with a pancreatic cyst that requires surveillance will be included from August 2015 until July 2024. Follow-up will continue until July 2025. The first analysis will be conducted in August 2020 to provide data for the MISCAN model.

Figure 2 Study Flowchart (1)



§ MISCAN = Microsimulation screening analysis

4. STUDY POPULATION

4.1 Population

This study will concern individuals with a pancreatic cyst, either, newly or previously diagnosed or previously operated upon, that warrants surveillance. Generally, asymptomatic cysts are detected coincidentally, on imaging studies performed for other indications. Based on a reported incidence rate of 2.4%, there are an estimated 200.000 eligible individuals in the Netherlands, mostly over 40 years old (6). Patients will be recruited in the Netherlands through the network of the 'Dutch Pancreatic Cancer Group' (DPCG) and the 'Dutch Pancreatitis Study Group', internationally through the members of the 'European study group on cystic tumours of the pancreas.

4.2 Inclusion criteria

- Individuals with a pancreatic cyst (either newly or previously diagnosed, or previously operated upon)
- Cyst surveillance is warranted, according to the treating physician
- Age >18
- Informed consent

4.3 Exclusion criteria

- History of chronic pancreatitis
- Suspected pseudocyst (simple, thin walled cyst that developed in the course of acute (necrotising) pancreatitis, as documented by sequential imaging studies)
- Suspected serous cystadenoma (typical microcystic lesion with lobulated outlines and a calcified central scar, and cyst fluid CEA levels < 5 ng/ml)
- Von Hippel-Lindau disease
- Limited life expectancy (< 2 years)

4.4 Sample size calculation

In total, we aim to include 5000 patients during the study period of 10 years, of which 250 patients per year will be included in the Netherlands. This will provide over a 1000 patient years after three years, even in the case of expected loss to follow-up (15% of patients included in the first year, 10% of those included in the second year, and 5% included in the third year). Internationally, depending on the number of cooperating centres throughout Europe, we expect to include between 250 and 500 patients yearly.

5. TREATMENT OF SUBJECTS

5.1 Diagnostic work-up before inclusion

The goal of the diagnostic work-up is to characterize the cyst and to rule out malignancy. This work-up should have taken place no more than 6 months prior to inclusion. In accordance with the European guidelines, evaluation with either Magnetic Resonance Imaging/Magnetic Retrograde Cholangiopancreatography (MRI/MRCP) or Endoscopic Ultrasound (EUS) is preferred. In case of inconclusive EUS results, fine needle aspiration (FNA) or fine needle biopsy (FNB) might be performed, according to the judgement of the endoscopist. In addition, the guidelines recommend determination of serum CA19-9 (with or without fasting glucose and glycated Hemoglobin A1c) at each follow-up moment.

5.2 Inclusion and cyst surveillance

If cyst follow-up is warranted according to the treating physician and in- and exclusion criteria are met, a patient is eligible for the study. Cyst surveillance will take place at the hospital of origin, and will be coordinated by the treating physician. The advised surveillance strategy is based on the European guidelines, and consists of imaging studies (MRI/MRCP or EUS), every 6 to 12 months, and determination of serum CA 19.9 (Figure 1, see also paragraph 6.3, study procedures)(2). Determination of glucose and HbA1c is recommended.

5.3 Cyst management during follow-up

During follow-up, the treating physician is responsible for patient management and decision-making. If follow-up parameters change during follow-up, the decision for a more elaborate diagnostic work-up, surgery, or an intensified follow-up schedule is at the discretion of the treating physician. If the treating physician requires support or advice on such decisions, the PACYFIC study team offers the possibility to consult a panel of experts, online. The panel is only accessible for Dutch physicians.

5.4 Biomaterial collection

Only in the Erasmus University Medical Center, and only in a minority of patients (see chapter 8 for criteria), secretion of pancreatic juice will be stimulated during EUS evaluation, by infusing intravenous human synthetic secretin (ChiRhoStim®, ChiRhoClin Inc. (Burtonsville, Maryland, USA), provided by Tramedico B.V. (Weesp, the Netherlands)), at a dose of 0.2 µg/kg over 1 minute. The secreted

pancreatic juice is collected from the duodenal lumen by suctioning the fluid through the endoscopic channel.

Determination of CA19.9 is performed as recommended in the EU guidelines. On the other hand, glucose and HbA1c determination is decided by the treating physician. Each center can choose whether to participate with the collection of blood for the PACYFIC biobank. If participating, the center can choose between the collection of 2 tubes (serum and EDTA), or 4 tubes (2x serum, EDTA and cell-save tube).

5.5 PACYFIC Expert panel

The Expert Panel consists of a team of ten highly specialized gastroenterologists, surgeons, and radiologists. The panel can be consulted by all Dutch physicians (participation in the study is not mandatory). The consultation takes place in a web-based, secured environment, which can be accessed through the website with a personalized login. The consulting physician will first be asked to agree to the expert panel disclaimer (Addendum, Text 1). Next, he or she will be able to upload patient information and imaging studies. The members of the expert panel will be notified by email to login to the consultation. After one week, the consulting physician will be informed by email of the answers of at least three experts.

Consulting an Expert Panel is regarded as a second opinion, and thus, as part of standard patient care. Therefore, informed consent is not required. Patient information will only be saved during the consultation process and automatically deleted as soon as a final answer was given. However, the outcome of the consultations will be stored anonymously in the study database, to evaluate the responses of the expert panel. These procedures were thoroughly discussed with and approved by the security officer and judiciary department of the Erasmus MC.

5.6 Data collection

Treating physicians will be asked to fill out an online case record form regarding the choice and outcome of the imaging studies, serum and cyst fluid analysis, and the clinical condition of the patient. Patients will fill out questionnaires regarding their quality-of-life and the burden of cyst surveillance.

Any cyst related event will be recorded (i.e. changes in follow-up parameters or strategy, additional imaging studies, reaching an indication for cyst resection, the decision for or

against treatment (with motivations), surgical procedures, complications of surgery, pathological outcome). If conservative management is chosen although resection criteria are met, the argumentation for this decision will be noted. Cyst follow-up will be continued in this group and the subsequent outcome will be monitored. Data collection will continue until July 2024. The study database will not only be used to store recorded data, but will also automatically generate reminders to the treating physician, regarding follow-up dates.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

Wash-out of pancreatic juice will be stimulated by infusing intravenous human synthetic secretin (ChiRhoStim®, ChiRhoClin Inc, Burtonsville, MD, United States), provided by Tramedico B.V. (Weesp, the Netherlands). Secretin is a hormone that is normally released from the duodenum upon exposure to gastric acid, fatty acids or amino acids (food intake) (17). It was FDA approved years ago in the United States (April 9, 2004), and approved by the Inspection of Healthcare in the Netherlands for the diagnostic use in patients with a focal lesion of the pancreas in 2017.

7.2 Summary of findings from literature and potential risks and benefits

Porcine secretin has been used for decades, especially during MRCP, to visualise the pancreatic ductal system. Because of limited availability, human synthetic secretin was developed as an alternative (ChiRhoStim®). It is identical to biologic human secretin and differs from porcine secretin at two amino acid positions: 14 (glutamic acid vs aspartic acid) and 16 (glycine vs. serine). It eliminates the risk of an allergic response in patients hypersensitive to porcine products and is in this sense superior(18).

Few side effects have been reported, these include: increased pancreatic enzyme levels (amylase, lipase, trypsine) in blood (common: 1/100-1/10), electrolyte disturbance in case of long-term administration (uncommon: 1/1000 to 1/100; e.g. acidosis, hyponatraemia and hypocalcaemia are never seen), and diarrhoea (rare: 1/10.000 to 1/1000). An overdose may lower blood pressure, yet acute poisoning has never been reported. Notable are the studies, published by the Johns Hopkins group (Baltimore, MD), who applied human synthetic secretin in a similar setting as our study, and never encountered any (serious) adverse events related to secretin infusion (17, 19-27).

7.3 Dosages, dosage modifications and method of administration

A dosage of 0.2 µg/kg over 1 minute will be infused intravenously. This is the unmodified dosage as prescribed by the manufacturer. This will result in 5-10 ml pancreatic juice (collected in 5 minutes) after 5 minutes. All patients undergoing an EUS in the Erasmus University Medical Center already receive intravenous access prior to procedure, so there is no additional patient burden.

7.4 Preparation, labelling and drug accountability

Tramedico B.V. (Weesp, the Netherlands) will provide the human synthetic secretin in 16mcg vials. The trial pharmacy will be responsible for the drug accountability and the

delivery of the secretin vials at the endoscopy department of Erasmus University Medical Center. The required vials will be stored temporarily in a fridge (2-8 °C) at the endoscopy department prior to administration.

The pharmaceutical company Tramedico B.V. will only provide the secretin required for the collection of pancreatic juice. Tramedico B.V. is not a sponsor of this study, and no financial agreements or sponsorship agreements exist between Tramedico B.V. and the investigators. Tramedico B.V. will not get access to the study results.

8. METHODS

8.1 Study endpoints

8.1.1 Main study endpoints

- The number of patients who reach an indication for pancreatic cyst resection, based on the criteria of the European evidence-based guidelines(1) (specified in Table I).
- The number of patients, diagnosed with a malignant cyst (either high-grade dysplasia or carcinoma).

8.1.2 Secondary study endpoints

- The outcome of patients with an indication for cyst resection (treated and non-treated), in terms of the number of operated patients, surgical procedures, morbidity, mortality, and cyst recurrence (Table II and III).
- Cyst evolution, in terms of development of symptoms, cyst growth, nodules, and secondary pancreatic duct dilatation.
- The perceived burden of surveillance for participants, as assessed by questionnaires regarding attitude towards surveillance and general anxiety and depression (Hospital Anxiety and Depression scale, HADS) (Table V) (28-32).

8.1.3 Other study endpoints

- To identify possible risk factors for malignancy, either patient or cyst related (Table IV).
- To identify useful biomarkers for malignancy
- To design more efficient and cost-effective surveillance strategies, by building a micro-simulation screening analysis (MISCAN) model, based on the outcome data of this study.

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

After informed consent is obtained, baseline characteristics will be filled out on the on-line CRF (patient and cyst characteristics, previous pancreatic surgery).

Follow-up schedule and imaging studies

Cyst surveillance will take place at the hospital of origin. The treating physician will coordinate the surveillance and will be reminded about follow-up dates by email. Follow-up management is at the discretion of the treating physician. According to the European guidelines, cyst surveillance is recommended at one-year intervals, except for newly diagnosed cysts, for whom 6-months intervals are advised during the first year. The guidelines advise to perform surveillance by MRCP, with EUS as an alternative. The local radiologist is provided with instructions regarding the aspects that need to be addressed in the imaging reports. If patients have more than one cyst, worrisome features will be monitored for each cyst.

To ascertain the reproducibility and quality of the MRI reports, 100 imaging studies will be selected at random and sent to the Erasmus University Medical Center, for re-evaluation by a radiologist (TB). Discrepancies will be recorded and used to calculate the inter observer variability.

Pathological analysis and tissue handling

If obtained, cyst fluid should be sent out to the laboratory for biochemical analysis (CEA, CA 19.9, amylase). The rest of the cyst fluid will be send to the department of pathology for standard diagnostic work-up. Here, it will be centrifuged to obtain a deposit to process a smear and/or cellblock. All remnant cyst fluid that is left after standard diagnostic work-up (either, supernatant or pure cyst fluid), should be stored and frozen at -80 °C for future molecular analysis. This step can be omitted in centers without such freezing facilities.

The pathologist will be provided with a protocol regarding the aspects that need to be addressed in the pathology report. On request, the pathologist of the investigators team (KB) can be consulted for advice or a second opinion. If surgery is performed, a glass slide of the pathological specimen (or a histological sample, preserved in formalin) must be sent to the pathology department of the Erasmus Medical Center in Rotterdam, for revision.

Laboratory investigations

To determine the serum CA 19.9 level, a blood sample of at least 6 ml must be collected. For each hospital, the local laboratory technique and cut-off value for CA 19.9 will be applied and recorded. In addition, for future testing, four additional blood tubes will be

drawn (one 10 ml cell-save tube, one 6 ml EDTA tube, two 10 ml serum tubes) and stored at -20 and -80 °C. This part of the study is optional, a center can also choose to collect two tubes (one 6 ml EDTA tube, one 10 ml serum tube). Participation in the study is also possible without collection of biomaterials.

Pancreatic juice is collected during EUS (as described in chapter 5 and 7), solely at the Erasmus University Medical Center Rotterdam in patients that meet the following criteria: suspected diagnosis of IPMN (i.e. either multi-focal disease or confirmed pancreatic duct connection) AND either size ≥2cm or worrisome/high-risk features. If performed, pancreatic juice is snap frozen in dry ice and transported to the laboratory of Gastroenterology and Hepatology and stored in the PACYFIC biobank in -80 °C for future analysis.

Collection and storage of samples

All human samples that are collected during the study will be stored locally. If local facilities are not sufficient, samples may be sent to the Erasmus University Medical Center Rotterdam, for storage.

Patient questionnaires

Patients will be asked to fill out a questionnaire at home (Table V). This questionnaire will be sent to them by email, directly after inclusion and after each follow-up visit. Participation in the questionnaires is optional; patients can voluntarily provide their email address for this purpose. The questionnaire is filled out on-line, which will take approximately 5 to 15 minutes. Patients who fail to respond to the questionnaire will be reminded by email after two weeks, and the invite e-mails will have an opt-out option. The questionnaires will be installed in the Dutch, English, German, Spanish, and Italian language. If the native language of the participant is not available, the questionnaire will be translated to the specific language.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences.

8.4.1 Specific criteria for withdrawal

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

These subjects will receive routine care from their treating physician.

8.7 Premature termination of the study

Not applicable

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigator will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

No specific serious adverse events are expected. Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the surveillance protocol. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded and reported to the coordinating investigator.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported by the coordinating investigator through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Not applicable

9.2.2 Annual safety report

Not applicable

9.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.4 Data Safety Monitoring Board (DSMB)

A special steering committee will be formed, consisting of an experienced gastroenterologist and surgeon, who will guard the safety and efficacy of the study protocol, in the light of possible new findings or data. The committee will report to the principal investigators and the medical ethics committee when they suspect a substantial advantage or disadvantage for certain groups of participants or surveillance strategies.

10. STATISTICAL ANALYSIS

The first analyses will concern the data collected within the first three years (until 2018). This report will contain purely descriptive statistics, according to the study endpoints described in 6.1. The thus obtained outcome data will be used as input for the MISCAN model. The second analysis, after 10 years, will give an update of the first report and provide a more in depth analysis of the primary and secondary study endpoints.

10.1 Descriptive statistics

Baseline patient and cyst characteristics will be described (Table IV). Also, descriptive of the primary and secondary endpoints will be given. This will be performed for the total cohort and the following sub-populations: 1. unspecified cysts and suspected side-branch IPMN's, 2. newly and previously diagnosed cysts, and 3. cysts followed by EUS and MRCP. For each (sub) population, the follow-up duration, visit frequencies, and numbers lost-to-follow-up will be reported.

Depending on distributional properties of the observed variable, percentages, means ± standard deviations (SD), or medians with interquartile ranges (IQR) will be reported. Statistical significance will be assessed with use of the Student's t-test for normally distributed continuous data; either the chi-square test for categorical data (with Yates' correction when appropriate) or Fisher exact test for categorical data; and the median test for non-normally distributed continuous data. All reported p-values will be two-sided and a value < 0.05 will be considered to be significant. Data will be analysed with SPSS 22 (or newer), Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois).

10.2 Univariate analysis

For the primary endpoints, univariate comparisons will be conducted, to identify individual patient and cyst risk factors for malignancy (Table IV). As primary potential risk factors are considered; 1. Cyst size, 2. Cyst growth, 3. Mural nodules/solid components, 4. increased serum CA 19.9, 5. Pancreatic duct dilatation, and 6. Patient age. Survival analysis techniques and Cox regression with time-dependent recurrent covariates measures will be applied to assess significance.

10.3 Multivariable analysis

Multivariate survival analysis will only be performed if the number of events will be > 30. This is expected to be the case for the primary endpoint. The potential risk factors, given above, will have first interest. A statistical program (MPlus) will be used to perform

multilevel analysis of longitudinal data (repeated measures), to analyze changes over time for the different patient reported outcomes, such as cancer worries, anxiety, and depression(33).

10.4 Interim analysis

Is described above as the first analysis report

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (sixth version, 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

The treating physician will inform eligible patients about the study and will explain the aims, methods, anticipated benefits, and potential hazards. Also, this information will be provided in print. Subsequently, patients will have at least 48 hours to decide if they want to participate in the study, by giving their written informed consent. If patients have any further questions, they can consult an independent physician (MS in the Netherlands).

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

Participation to the study does not cause any risk for patients, because the surveillance schedule does not differ from the present follow-up recommendations. The only possible burden may be the fact that extra blood samples will be taken and that participants are invited to complete an online questionnaire after each visit. Completing the questionnaire will take no more than 5 to 15 minutes. There are no significant risks effects related to secretin use (see paragraph 7.2). However, the EUS procedure is prolonged by 5-10 minutes. Subjects may benefit from the active approach towards compliance to the cyst surveillance program. This will minimize the risk of patients getting lost to cyst follow-up.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance, in accordance with article 7, subsection 6 of the WMO.

Because the study is without risks, dispensation from the obligation to provide insurance for the participating subjects was granted by the METC of the Erasmus Medical Center.

11.6 Incentives

Not applicable

12. ADMINISTRATIVE ASPECTS AND PUBLICATION

12.1 Handling and storage of data and documents

12.1.1 Responsibilities of the investigator

The principal investigator is responsible for the conduction and completion of the study. The principal investigator ensures to have appropriate facilities and adequate staff that are fully instructed regarding the study protocol and study procedures.

12.1.2 Electronic Case Record Form (eCRF)

During the course of the study, all collected data will be recorded in an eCRF. The eCRF will be completed timely and fully, according to the protocol. The investigators are responsible for the quality of the data recording. In the event of a protocol deviation, the 'nature of' and 'reasons for' the deviation will be recorded in the hospital record. If the deviation is linked to the content of the CRF, the CRF will also be adjusted. The principal investigator of each participating center is responsible for visit approval.

12.1.3 Privacy rules

The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). All outcome data will be provided by the treating physician through a secured, online eCRF. Patients will be identified in the eCRF by study-number. The investigators will keep an identification log, consisting of the information to link source records to the eCRF.

Patients will complete their questionnaires online. For this purpose, patients will be asked to provide their email address in the informed consent form. This e-mail address will be stored in a separate database, and will only be used to send an email to the patient, which will include an option for the patient to opt-out of future e-mails. The link between e-mail address and patient is not visible for unauthorized persons and will only be used to serve as an identification key for the electronic system, to be able to couple the study number in the main eCRF to the corresponding respondent in the questionnaire database.

The data are stored and processed using a database program for personal computers. Anonymous data are stored separately from identifiable data (i.e. a patient's email address), so that it is impossible to couple research data to specific individuals. All data that leaves the investigational site will be blinded and

anonymized. Only authorized study team members are able to view certain non-anonymous data. For analysis, the anonymous study data from both the clinical and the questionnaire database will be exported and subsequently coupled. From this overall mother-database, data will be transferred to a statistical program. Only anonymized data will be transferred to the statistician for further analysis.

The subjects will be informed that the data will be stored on paper and electronically, that local regulations for the handling of computerized data will be followed as described in the written patient information, and that identification of individual patient data will only be possible for the coordinating and principal investigator. Furthermore, the subjects will be informed about the possibility of inspections of relevant parts of the hospital records by health authorities. These officials will be identified and have signed a confidentiality agreement.

12.1.4 Archiving of data

Patient identification log, hospital records (source documents), informed consent forms, and clinical databases must be kept for at least 15 years after completing the study. If the principal investigator and/or coordinating investigator moves or retires, he/she must nominate someone in writing, to be responsible for record keeping. Archived data may be held on electronic record, provided that a back-up exists and a hard copy can be obtained, if required.

12.2 Monitoring and Quality Assurance

See paragraph 9.4.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is set in July 2025, when the 10-year follow-up period has ended. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The rules for public disclosure and the publication policy are formulated in the "Consortium Agreement of the PACYFIC study group; rules for publication, authorship and ownership of data".

12.7 Authorship rules

See paragraph 10.5

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12. ADDENDUM

Text 1: Online disclaimer Expert Panel

"Deze website is tot stand gekomen op initiatief van het Erasmus MC. Middels deze website wordt raadpleging van het PACYFIC expert panel mogelijk gemaakt. Het is uitsluitend zorgverleners toegestaan dit expert panel te raadplegen. Gebruik van deze website en meer in het bijzonder raadpleging van het panel komen volledig voor risico van de betreffende zorgverlener en het Erasmus MC aanvaardt dan ook geen aansprakelijkheid voor de inhoud van deze website en meer in het bijzonder de raadpleging van het expert panel. Onder raadpleging van het panel wordt mede begrepen de verwerking van de in dit kader toegezonden (medische) informatie alsmede het gebruik van het door het panel gegeven advies. Door op "akkoord" te klikken verklaart u deze disclaimer te hebben gelezen en akkoord te gaan met de inhoud daarvan."

(Deze disclaimer is opgesteld in samenwerking met Andre Domevscek, afdeling Juridische zaken Erasmus MC).

Table I: Resection criteria, as recommended in the consensus statement by the European study group on cystic tumours of the pancreas (2).

Resection criteria for cystic neoplasms of the pancreas		
1. Cysts ≥ 4 cm in size 2. Cysts diagnosed as - Mucinous Cystic Neoplasm (MCN) - Main-duct Intraductal Papillary Mucinous Neoplasm (MD-IPMN), - Mixed-type Intraductal Papillary Mucinous Neoplasm (MT-IPMN) - Solid Pseudopapillary Neoplasm (SPN) 3. Presence of risk factors* for malignancy (≥1 absolute or ≥ 2 relative)		
Risk factors*	Absolute criteria	Relative criteria
Cyst related	Positive cytology for malignant/high grade dysplasia Solid mass Enhancing mural nodules (≥5mm) Main pancreatic duct dilation ≥10mm	Growth-rate ≥ 5mm/year Main pancreatic duct dilation (5-9.9mm) Cyst diameter ≥ 40mm Enhancing mural nodules <5mm
Patient related	Jaundice (tumor related)	Increased levels of serum CA19.9 (≥37 U/ml) New-onset of diabetes mellitus Acute pancreatitis (caused by IPMN)

Table II: Types of pancreatic cyst resection

Surgical procedure
Pylorus preserving pancreaticoduodenectomy or classic Whipple procedure
Duodenum preserving pancreatic head resection (Beger/Frey's procedure)
Distal pancreatectomy with/without splenectomy
Central pancreatectomy
Other

Table III: Predicted morbidity and mortality after surgical resection

Morbidity (Major complications)	Mortality
Pancreatic fistula Anastomotic leak Postoperative bleed Other complications requiring re-laparotomy	30- and 90-day postoperative mortality

Table IV: **Potential risk factors of malignancy; patient and cyst related**

Patient Characteristics	Cyst Morphology	Cyst Fluid
Age (years) Sex (M/F) History of pancreatitis History of pancreatic cyst/cancer History of pancreatic surgery Family history pancreatic cancer Family history of breast and/or colon cancer Steatorrhea New onset Diabetes Insulin use Smoking Alcohol abuse Serum CA 19.9 level	Number of cysts (Single/Multiple) Cyst size (bidirectional) Cyst growth Location (uncinate process, head, neck, body, or tail) Uni- or multiloculair Micro- or macrocystic pattern Cyst wall > 2 mm (Y/N) Solid components (if yes; enhancing?) Calcifications (if yes; central/peripheral) Pancreatic duct communication (Y/N) Main pancreatic duct dilatation (Y/N) Common bile duct dilatation (Y/N) Calibre change main PD (Y/N)	Presence Mucin Malignant cells Cytology CA 19.9 CEA Amylase

Table V: Patient Questionnaire

I. History and background (to evaluate risk factors)
New onset Diabetes, and insulin use
History of pancreatitis, pancreatic cysts/cancer/surgery
Smoking and drinking habits
Family history of pancreatitis, and breast/colon or pancreatic cancer
II. Questions regarding participants' knowledge of their pancreatic cyst
Knowledge of type of cyst
Knowledge of chance of progression of cyst to malignancy
Having searched for additional information on their pancreatic cyst
III. Questions regarding the general burden of surveillance and cancer worries
Regular checking of a pancreatic cyst…
- Reduces my concerns about developing pancreatic cancer
- Gives me a sense of certainty.
- May lead to unnecessary worries.
- Is a good method to detect cancer in time.
To what extent…
- Do the follow-up visits convey you a sense of security?
- Are you nervous when you have to come for your check-up visit?
- Are you reassured after the follow-up visit?
- Did you sleep less well in the week before follow-up?
- Did you postpone plans until after the follow-up visit?
- Do you find the regular follow-up burdensome?
- Do the advantages of the check-up outweigh the disadvantages for you?
- Would you be more worried about your cyst if it was not checked regularly?
- Do you dread the next check-up visit?
- Would you prefer your cyst to be checked less frequently?
How often would you like to have your pancreatic cyst checked?
For how long would you like to be checked?
Has your fear for the development of pancreatic cancer changed, now you know tha
your cyst will be followed?
How would you feel if pancreatic cyst follow-up was no longer advised, because the

risk of developing pancreatic cancer is too low?
IV. Worries and burden of investigational procedures Burden of imaging (MRCP/EUS/CT)
V. Hospital Anxiety and Depression Scale I feel tense or wound up. I still enjoy the things I used to enjoy. I get a sort of anxious feeling, like something bad is about to happen. I can laugh and see the funny side of things. Worrying thoughts go through my mine. I feel cheerful. I can sit at ease and feel relaxed. I feel as if I am slowed down. I get a sort of anxious feeling, like butterflies in my stomach. I have lost interest in my appearance. I feel restless, as if I have to be on the move. I look forward with enjoyment to things. I get sudden feelings of panic. I can enjoy reading a good book or watching a radio or TV programme.