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

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

Version 2, September 2014

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PROTOCOL TITLE Pancreatic Cyst Follow-up, an International Collaboration

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Laboratory sites	Department of Clinical Pathology Hospital……
Pharmacy	Not applicable

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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 most deadly 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 experts consensus statement, 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 3 years.

Study population: Patients with a pancreatic cyst - either newly or previously diagnosed - 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 consensus statement, 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.

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 [1, 2]. The only burden for participating patients may be providing two additional blood samples and filling out an online questionnaire during follow-up. 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[3]. 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%[4]. In healthy individuals undergoing a screening MRI, we found a pancreatic cyst in 2.4%[5]. An autopsy series by Kimura even reported a prevalence rate of 24%[6].

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[7, 8]. Unfortunately, to distinguish these pancreatic cysts, especially the smaller ones, is often impossible[9].

A second problem in pancreatic cyst management is that data regarding the natural history and predictive factors for malignant degeneration are virtually lacking.[2, 10]. The literature is biased by highly selected patients series from tertiary referral centres. Sahani reported a 13% risk of malignancy in cysts smaller than 3 cm[2]. In asymptomatic cysts, the reported prevalence of carcinoma varies between 1 and 3%[8]. 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[7]. 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[5].

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 most deadly cancers.

In 2012, a group of European experts (European study group on cystic tumours of the pancreas) formulated a consensus statement regarding the management of pancreatic cystic neoplasms[1]. These non-evidence based 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, the panel recommends 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 evidence-based data, most likely, this surveillance advice will be widely implemented in clinical practice. Therefore, these recommendations require prompt validation by a prospective cohort study.

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[11-13]. 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[14].

2. OBJECTIVES

Primary objective

To establish the yield of regular pancreatic cyst surveillance, based on a recently published European experts consensus statement, in terms of identified patients that require cyst resection, diagnosed malignancies, cyst evolution, and the perceived burden for participants.

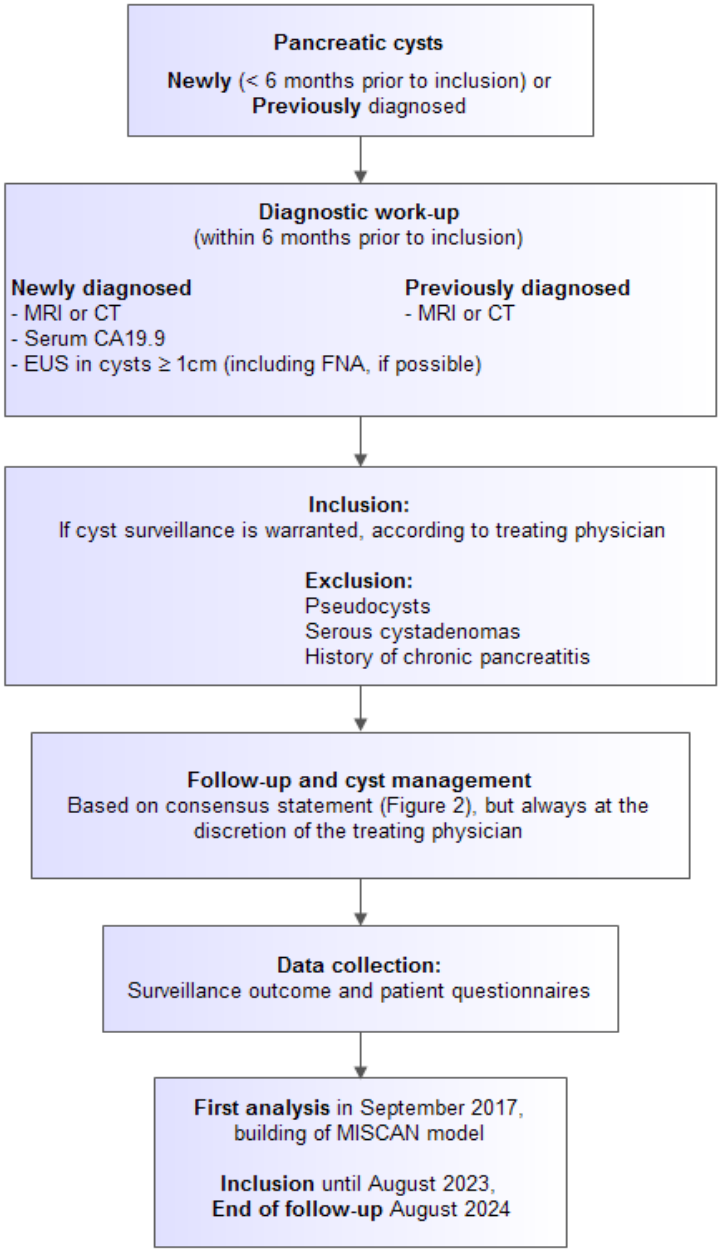
Secondary objective

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 September 2014 until August 2023. Follow-up will continue until August 2024. The first analysis will be conducted in September 2017, after three years, to provide data for the MISCAN model.

Figure 1; Study Flowchart



4. STUDY POPULATION

4.1 Population

This study will concern individuals with a pancreatic cyst, either newly or previously diagnosed, that warrant 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 [5]. Patients will be recruited in the Netherlands through the network of the 'Dutch Pancreatic Cancer Group' (DPCG) and the 'Dutch Pancreatitis Study Group', and 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)
- 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. A high quality cross-sectional imaging study, either Computed Tomography (CT) or Magnetic Resonance Imaging (MRCP) should always be performed. (based on the consensus statement, MRCP is preferred). In addition, in new cysts (diagnosed less than 6 months prior to inclusion), serum CA 19.9 should be determined. New cysts over 1 cm in size should also be evaluated by endoscopic ultrasonography (EUS), with fine needle aspiration (FNA), if technically feasible.

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 consensus statement, and consists of imaging studies (MRCP or EUS), every 6 to 12 months, and determination of serum CA 19.9 (Figure 2, see also paragraph 6.3, study procedures)[1].

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.

5.4 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 August 2024. The database will not only be used for data analysis, but will also automatically generate reminders to the treating physician, regarding follow-up dates.

6. METHODS

6.1 Study endpoints

6.1.1 Main study endpoints

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

6.1.2 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) [15-19].

6.1.3 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.

6.2 Randomisation, blinding and treatment allocation

Not applicable

6.3 Study procedures

After informed consent is obtained, the treating physician will receive online information regarding the surveillance strategy, as formulated in the consensus statement (Figure 2). Baseline characteristics will be filled out on the on-line CRF (patient and cyst characteristics, previous pancreatic surgery). The surveillance will take place at the hospital of origin. The treating physician will coordinate the surveillance. They will be reminded about follow-up dates by email.

Follow-up schedule and imaging studies

Follow-up is recommended at one-year intervals, except for newly diagnosed cysts with a diameter of ≥ 1 cm, for whom 6 months intervals are advised during the first year. According to the consensus statement, the follow-up frequency should increase after 5 years, to every 6 months. However, as this particular recommendation lacks all scientific justification, the decision to increase the follow-up frequency of the study population will not be made until 2017, after a preliminary analysis is performed.

Based on the consensus statement, cyst surveillance will be performed by MRCP. EUS will serve as an alternative, according to the preference of the treating physician. Switches in follow-up modality are permitted. The local radiologist is provided with instructions regarding the aspects that need to be addressed in the imaging report. If patients have more than one cyst, the specifications of the three largest cysts will be recorded and worrisome features will be monitored for all cysts.

To ascertain the reproducibility and quality of the MRI reports, 100 imaging studies will be selected at random and sent to the Erasmus Medical Center, for re-evaluation by a radiologist (TB). Discrepancies will be recorded and used to calculate the inter observer variability. For this reason, imaging studies should be stored at the hospital of origin. On request, during the study, this radiologist (TB) can be consulted for advice or a second opinion, in case of diagnostic difficulties.

Pathological analysis and tissue handling

The pathology department will handle the cyst fluid; at least 0.5 ml is centrifuged to generate deposit and supernatant fluid. The deposit will be used to process a smear and/or cellblock, for pathological analysis. The supernatant fluid will be sent out to the laboratory for biochemical analysis (CEA, CA 19.9, amylase). If at least 0.5 ml of the cyst fluid is left after the above mentioned procedures, this should be stored and frozen at

minus 80 degrees Celsius, for future molecular analysis. This step will 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 genetic testing, two additional 6 ml blood samples will be drawn (one EDTA, one Serum tube) and stored at –20 and -80 degrees Celsius, respectively. This only applies for participating centers with such facilities.

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 with a newly diagnosed cyst will be asked to fill out a questionnaire at home (Table V). This questionnaire will be sent to them by email (if they gave permission to do so) at study entry, after every follow up visit for the first three years, once after 5 and 10 years, and after cyst related events. The questionnaire can be 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. Patients who do not want to provide their email address will be able to join the study, without participating in the questionnaire evaluation.

6.4 Withdrawal of individual subjects

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

6.4.1 Specific criteria for withdrawal

Not applicable

6.5 Replacement of individual subjects after withdrawal

Not applicable

6.6 Follow-up of subjects withdrawn from treatment

These subjects will receive routine care from their treating physician.

6.7 Premature termination of the study

Not applicable

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs that makes the disadvantages of participation appear significantly greater than was foreseen in the research proposal. The study will be suspended, pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 Adverse and serious adverse events

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.

7.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Not applicable

7.2.2 Annual safety report

Not applicable

7.3 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.

7.4 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.

8. STATISTICAL ANALYSIS

The first analyses will concern the data collected within the first 3 years (until 2017). 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. In addition, these data will be used to determine if the surveillance interval must be increased after 5 years of follow-up, to every 6 months, as was suggested in the consensus statement. 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.

8.1 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).

8.2 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.

8.3 Multivariate 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[20].

8.4 Interim analysis

Is described above as the first analysis report

9. ETHICAL CONSIDERATIONS

9.1 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).

9.2 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).

9.3 Objection by minors or incapacitated subjects

Not applicable

9.4 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 two extra blood samples will be taken and that participants with a newly diagnosed cyst are invited to complete an online questionnaire. Completing the questionnaire will take no more than 5 to 15 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.

9.5 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.

9.6 Incentives

Not applicable

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

10.1.1 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.

10.1.2 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.

10.1.3 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 email address will be stored in a separate database, and will only be used to send an email to the patient after every visit. The link between email 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 patients 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.

10.1.4 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.

10.2 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.

10.3 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.

10.4 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 August 2024, 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.

10.5 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".

10.6 Authorship rules

See paragraph 10.5

11. REFERENCES

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12. ADDENDUM

Figure 2; Flowchart of pancreatic cyst surveillance, based on the recommendations of the consensus statement by the European study group on cystic tumours of the pancreas[1].

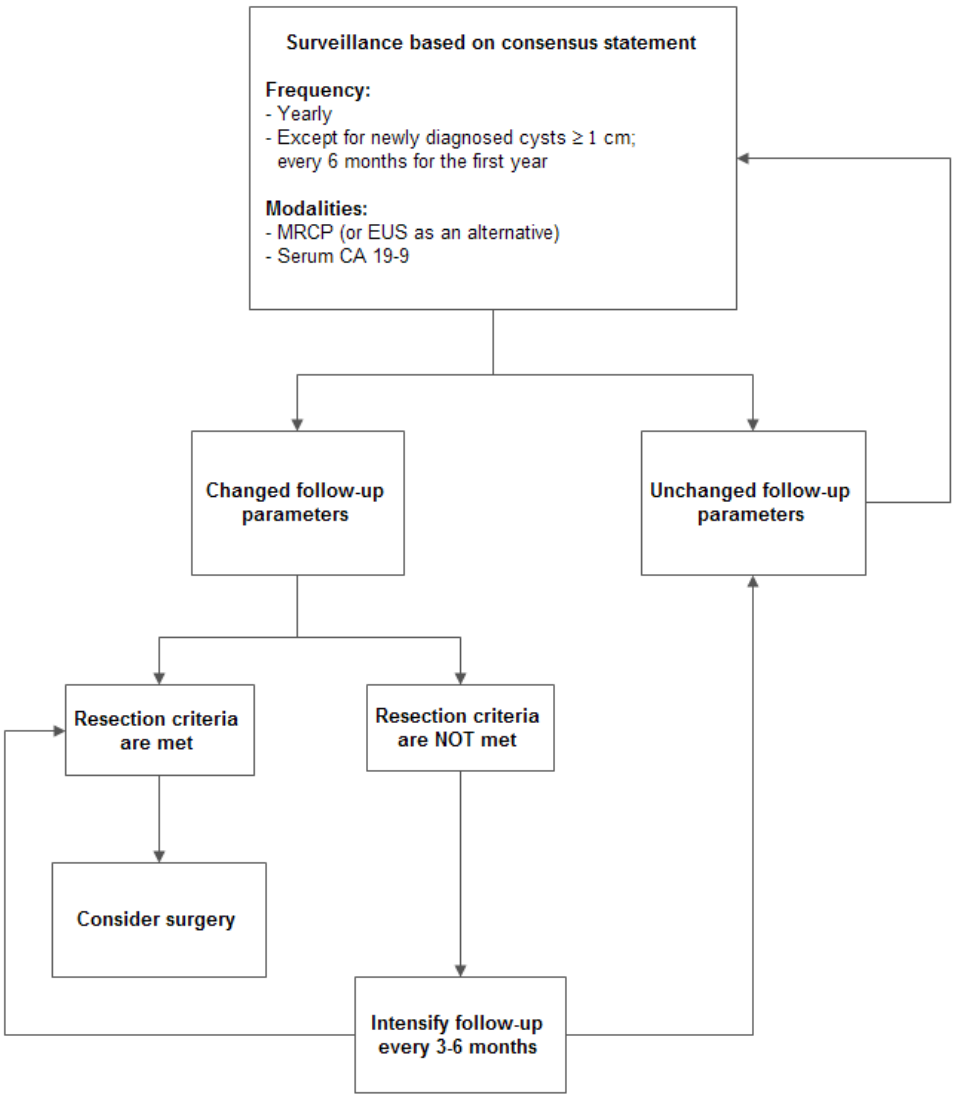

Table I: Resection criteria, as recommended in the consensus statement by the European study group on cystic tumours of the pancreas [1].

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)), - Solid Pseudopapillary Neoplasm (SPN) - 3. Presence of risk factors* for malignancy (≥1 absolute or ≥ 2 relative)		
*** Risk factors**	**Absolute criteria**	**Relative criteria**
Cyst related	- Mural nodules - Dilatation Main Pancreatic Duct (MPD) > 6 mm - Eggshell calcifications	- Significant growth
Patient related	- Jaundice - Acute pancreatitis - Diabetes	- Elevated serum CA 19.9 - Epigastric pain - Weight loss

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)	Number of cysts (Single/Multiple)	Presence Mucin
Sex (M/F)	Cyst size (bidirectional)	Cytology
Body Mass Index (BMI)	Cyst growth	CA 19.9
History of pancreatitis	Location (head, neck, body, or tail)	CEA
History of pancreatic cyst/cancer	Micro- or macrocystic pattern	Amylase
History of pancreatic surgery	Uni- or multiloculair	
Family history pancreatic cancer	Internal septa (if yes, enhancing?)	
Family history of breast and/or	Cyst wall (thick > 2 mm/thin < 2 mm)	
colon cancer	Solid components (if yes; enhancing?)	
Symptoms of steatorrhea	Calcifications (if yes; central/peripheral)	
Diabetes	Pancreatic duct communication (Y/N)	
Insulin use	Main pancreatic duct dilatation (Y/N)	
Smoking	Common bile duct dilatation (Y/N)	
Alcohol abuse	Calibre change main PD (Y/N)	
Serum CA 19.9 level		

Table V: Patient Questionnaire

I. History and background (to evaluate risk factors) Height and weight Smoking and drinking habits History of pancreatitis, pancreatic cysts/cancer/surgery, Diabetes, and insulin use Family history of pancreatitis, and breast/colon or pancreatic cancer
II. Worries and burden of investigational procedures Burden of imaging (MRCP/EUS/CT)
III. Questions regarding the general burden of surveillance and cancer worries Regular checking of a pancreatic cyst… - Is a good way to detect cancer in time. - Lessens my fear to get cancer. - Gives me a sense of security. - Can lead to unnecessary uncertainty. - Is not important to me, since it will be too late to change the outcome of the disease anyway To what extent… - Do you find the check-ups burdensome? - Do the advantages of the check-up outweigh the disadvantages for you? - Are you nervous when you have to come for your check-up visit? - Do you dread the next check-up visit? How often would you like to have your pancreatic cyst checked? For how long would you like to be checked? Did the cyst surveillance change the extent to which you worry about cancer?
IV. 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 frightened feeling, as if 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 frightened feeling, like butterflies in my stomach.
I have lost interest in my appearance.
I feel restless and 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.