

**CAPS Registry**

**Example answers for local review board approval**

**NOTE:** *The CAPS registry is an international multicenter observational registry. It is designed to record the outcomes of different clinical programs and research protocols, designed and executed by each participating center individually. As such, no review board approval is necessary for the participation in the CAPS registry and it does not require additional insurance.*

*This document contains standardized example answers which are meant to offer assistance to participating centers for their local review board approval. It is not obligatory to use any of the given answers for the local protocol.*

1. SUMMARY

**Rationale:** Evidence is beginning to accumulate that screening of individuals at high risk for pancreatic ductal adenocarcinoma (henceforth referred to as pancreatic cancer) leads to the detection of non-invasive precursor lesions and asymptomatic early stage cancer. Though these results are promising, data that ultimately prove that surveillance is truly effective in reducing morbidity and mortality are currently lacking. **Objective:** To determine whether a surveillance program consisting of <SPECIFY SURVEILLANCE STRATEGY> in a cohort of high-risk individuals results in an excess number of detected and surgically resected high-grade premalignant lesions and early stage pancreatic cancers compared to the natural disease development and manifestation. **Study design:** Single center prospective cohort study

**Study population:** Individuals with a familial or inherited ≥10-fold increased risk for developing pancreatic cancer.

**Procedures:** Screening entails <annual> <endoscopic ultrasonography and MR imaging>. The follow-up interval will be adjusted to (1) 3 months is case of the detection of a lesion of unknown clinical significance or (2) 6 months in case of the detection of a cystic lesion with a diameter 10-30mm. Whenever a suspicious lesion is detected that meets the criteria for surgical resection, the patient will be discussed in an expert panel and/or referred to the department of surgery. Screening starts at the age of 50 years or at least 10 years younger than the age of the youngest relative with PC, whichever comes first. Screening ends at the age of 75 years.   
In addition, yearly blood sampling will be performed.

**Main study parameters/endpoints:** The excess number of detected and surgically resected high-grade premalignant lesions and early stage pancreatic cancers resulting from <annual> screening using <endoscopic ultrasonography and MR imaging> compared to the natural disease development and manifestation.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:** Burden: (1) yearly screening investigations (EUS and MRI), (2) yearly blood sampling. Risk: (1) complications directly related to the screening procedure (EUS/MRI), (2) screening related drawbacks being over-diagnoses, false positive test results, and false negative test results. Benefits: (1) early disease detection and thereby reduction of pancreatic cancer related mortality, gains in life years and preventing people from dying of pancreatic cancer. Group-relatedness: not applicable.

1. INTRODUCTION AND RATIONALE
   1. The clinical burden of pancreatic cancer

Pancreatic cancer (PC) has a low age-adjusted incidence of 13.5 per 100,000 per year [1], yet is the fourth leading cause of cancer-related death in the United States, with an estimated 50,000 deaths in 2016. Mortality has been increasing by 0.4% each year, and in 2030, it is projected to be the second leading cause of cancer-related death [2, 3]. PC has a dismal prognosis, with a 5-year survival rate of 7%. Because surgery provides the only cure, survival greatly depends on operability at diagnosis. After surgery, the 5-year survival rate increases to 27%. However, only 15-20% of patients present with resectable disease and even in resected cases, 24% experience recurrence [4]. Earlier detection of PC would increase the chances of survival. It is estimated that precursor lesions require an average of 11.7 years to evolve into a malignant clone, and that metastatic subclones occur 6.8 years later [5]. This creates a window for early detection of PC cases through a surveillance program for high-risk individuals (HRIs).

* 1. High-risk individuals

The lifetime risk of PC in the United States’ general population is estimated at 1.5% [6]. Most PC cases are sporadic, but approximately 10% seems to be hereditary. A familial aggregation of PC has been demonstrated by both case-control and cohort studies [7]. In 3% of PC cases, this can be related to known genetic cancer susceptibility syndromes or inherited disease (table 1). In the remainder 7%, no underlying cause is found to explain the familial aggregation. This group is commonly referred to as familial PC (FPC) [7-9]. Individuals with at least one first-degree-relative (FDR) with PC are at higher risk (OR 1.76). This risk further increases in case of two or more FDR cases (OR 4.26). If a family contains two affected FDRs, the members of this family are defined as FPC kindreds. Prospective registries have shown that within FPC kindreds, risk increases rapidly according to the number of affected family members; 4.6-fold with one, 6.4-fold with two, and 32-fold with three affected FDRs [10]. FPC family members and carriers of known hereditary cancer syndromes are at a higher risk than the general population to develop PC. Therefore, they are designated candidates for surveillance.

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| --- | --- | --- | --- |
| Table 1. Genetic cancer susceptibility syndromes and inherited diseases with associated risk of PC | | | |
| Syndrome | **Gene(s)** | **Relative risk** | **Reference** |
| Peutz-Jeghers syndrome (PJS) | *STK11* | 132 | [11, 12] |
| Hereditary pancreatitis | *PRSS1* | 69 | [13, 14] |
| *SPINK1* | Unknown |  |
| Familial atypical multiple melanoma and mole (FAMMM) | *CDKN2A* | 46.6**§** | [15, 16] |
| Lynch syndrome | *MLH1/MSH2/MSH6* | 8.6-10.7≠ | [17-19] |
| Li Fraumeni syndrome | *TP53* | 7.3¥ | [20] |
| Familial adenomatous polyposis (FAP) | *APC* | 4.46 | [21, 22] |
| Hereditary breast and ovarian cancer (HBOC) | *BRCA2* | 3.5-22≠, **α** | [23-25] |
| *BRCA1* | 1-2.8**≠** | [24, 26] |
| *PALB2* | Unknown |  |
| Ataxia telangiectasia | *ATM* | 2.70 | [27] |
| § Does not include other mutation variations than p16-Leiden  ¥ Tested in *TP53* mutation carriers (tested or obligate) and their FDR with 50% chance on the mutation  ≠ Relative risk ranges between studies  α Upper limit measured as standardized incidence ratio instead of relative risk | | | |

* 1. Precursor lesions

Since surgery is the only curative treatment, surveillance is aimed to detect advanced precursor lesions or PC in an early, operable stage. Several precursor lesions have been identified: pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs). These precursor lesions are more common and of a higher grade in patients with a strong family history of pancreatic cancer than in patients with sporadic disease [28]. The ideal aim of surveillance is to detect all precursor lesions and specifically to identify those lesions with high-grade dysplasia and at high risk of malignant transformation [29].

## **International Cancer of the Pancreas Screening (CAPS) Consortium**

Many research questions need to be answered to confirm the feasibility and yield of screening and surveillance in high-risk individuals and to develop evidence-based screening protocols. For this, large cohorts are needed, but the numbers of screened high-risk individuals in each individual screening facility are too small. The ‘CAncer of the Pancreas Screening’ (CAPS) consortium is a unique collaboration, created to organize and facilitate research on surveillance for pancreatic cancer in high-risk individuals on a global scale. During the CAPS summit meeting in Baltimore, USA, in February 2011, it was concluded that an international registry should be developed in order to pool data from all participating centers [30].

1. OBJECTIVES
   1. Primary objective

* To determine whether a surveillance program consisting of <SPECIFY SURVEILLANCE STRATEGY> in a cohort of high-risk individuals results in an excess number of detected and surgically resected high-grade premalignant lesions and early stage pancreatic cancers compared to the natural disease development and manifestation.
  1. Secondary objective
* To determine whether above mentioned strategy results in an improved survival   
  compared to high-risk individuals not under surveillance and compared to the survival   
  statistics of sporadic pancreatic cancer.
* To determine patient and lesion characteristics by which precursor lesions can be stratified according their risk of malignant transformation.
* To determine the diagnostic yield of <SPECIFY USED MODALITIES, e.g. MR imaging and endoscopic ultrasonography (EUS)>
* <ADDITIONAL OBJECTIVES>

1. STUDY DESIGN

Single center prospective cohort study. The study will take place in a tertiary referral center, namely <SPECIFY CENTER>. The duration of the study is 5 years.

1. STUDY POPULATION
   1. **Study population**

This study will include individuals with a familial or inherited 10-fold risk for developing pancreatic cancer. This includes (1) first degree relatives (FDR) of familial pancreatic cancer-patients and (2) carriers of pancreatic cancer prone gene mutations.  
In order to include only individuals that are truly at risk of developing pancreatic cancer with an estimated 10-fold increased risk compared to the general population, all potential new inclusions will be extensively evaluated before inclusion. This evaluation includes (1) obtaining a detailed personal- and family medical history, (2) verification of clinical diagnoses reported by patients and family members, and (3) genetic testing for suspected gene mutation(s), based on the medical information.

* 1. Inclusion criteria

1. One of the following:

* Two or more affected blood relatives with PC, with at least one affected FDR
* Peutz-Jeghers syndrome (STK11 mutation or clinical diagnosis), regardless of family history
* p16 mutation carrier with ≥ 1 PC affected FDR
* BRCA2 mutation carrier with ≥ 1 PC affected FDR or two or more affected blood relatives
* PALB2 mutation carrier with ≥ 1 PC affected FDR
* Lynch syndrome with ≥ 1 PC affected FDR

1. 50 years of age or 10 years younger than the youngest PC case in the family  
   1. Exclusion criteria
2. Personal history of pancreatic cancer
3. Younger than 18 years of age
4. Older than 75 years of age
5. Unable to provide informed consent either due to mental retardation or a language barrier
6. Upper gastrointestinal tract obstruction or stricture that does not allow passage of an echoendoscope
7. Severe medical illness; (ASA score ≥ 3)
8. TREATMENT OF SUBJECTS
   1. Investigational product/treatment

Not applicable for this protocol.

* 1. Use of co-intervention

Not applicable for this protocol.

* 1. Escape medication

Not applicable for this protocol.

1. INVESTIGATIONAL PRODUCT

Not applicable for this protocol.

1. NON-INVESTIGATIONAL PRODUCT

Not applicable for this protocol.

1. METHODS
   1. Study parameters/endpoints

### **Main study parameter/endpoint**

* The excess number of detected and surgically resected high-grade premalignant lesions and early stage pancreatic cancers compared to the natural disease development and manifestation.

### **Secondary study parameters/endpoints (if applicable)**

* Mortality.
* The diagnostic yield of <SPECIFY USED MODALITIES, e.g. MR imaging and endoscopic ultrasonography (EUS)>.

### **Other study parameters (if applicable)**

* Patient characteristics: genetic background, date of birth, gender, race, education level, weight, height, personal history of diabetes, pancreatitis and cancer, smoking status, alcohol use, current medication use, family history of pancreatic and other cancers, symptoms of pancreatic pain, jaundice, steatorrhea or a thrombotic event.
* Lesion characteristics: type of lesion (solid, cystic, etcetera), location, size, signal intensity, border sharpness, ductal communication, calcification, vascular involvement, cyst wall thickness, cyst solid component.
* Ductal and parenchymal characteristics: common bile duct and pancreatic duct diameter; pancreatic duct: intraductal calcification, wall irregularity, wall echoicity, dilated side branches, stones; parenchym: hyperechoic foci or stranding, calcification, atrophy, enhanced lobularity.
* Laboratory results: glucose, HbA1c, CEA, CA 19-9, elastase.
* Cyst fluid results: CA 19-9, CEA, amylase, mucin.
* Treatment characteristics: neoadjuvant therapy, surgery (type, complications, re-operation), adjuvant therapy, palliative therapy.
* Pathology characteristics: number and type of lesions, level of dysplasia, histologic subtype, resection margins, TNM staging.  
  1. Randomisation, blinding and treatment allocation

Not applicable for this protocol.

* 1. Study procedures

### **Start and end of screening**

All individuals that are included in the study will be screened for pancreatic lesions using <yearly> <endoscopic ultrasonography (EUS) and MR imaging>. Screening starts at the age of 50 or 10 years younger than the age of the youngest relative with PC, whichever comes first. Screening stops at age 75.

### **Investigations**

EUS: Conscious sedation using midazolam/fentanyl or propofol will be applied. Systematic assesments will be made for the presence of pancreatic abnormalities being (1) focal lesions, (2) parenchymal changes and (3) ductal changes. The head and neck of the pancreas are assessed from the second portion of the duodenum and the bulb, the body and tail of the pancreas are visualized from the stomach.  
In case of the detection of an abnormality, fine needle aspiration (FNA) or fine needle biopsy (FNB) may be performed.  
  
MR imaging: MR imaging will be performed at minimum using a 1.5 Tesla machine (<SPECIFY BRAND>). The following sequences are obtained: T2 weighted axial series with and without fat saturation with 6 mm slices, 3D T2 heavy weighted coronal series with 1 mm slices for visualization of the pancreatic ductal system with axial reconstructions, diffusion weighted axial series with 8 mm slices using 3 different B-values (50, 400, and 800) including ADC-mapping, coronal TruFisp T2 weighted series with 5 mm slices, dynamic 3D T1 weighted (VIBE) series using 2 mm slices before and after intravenous contrast in arterial and portal phase.  
  
Blood sampling: Blood sampling will be done at a yearly basis. These samples will be stored for future studies to improve biomarker prediction of risk of high-individuals for progression to pancreatic cancer. Furthermore, levels of <fasten glucose and HbA1c> will be determined yearly. In addition, at baseline blood will be collected for DNA-isolation, both for future studies on biomarkers and to search additional pancreatic cancer susceptibility germline mutations.  
  
<ADDITIONAL MODALITIES / SALIVA SAMPLING / FECES COLLECTION>

### **Follow-up policy**

Patients will be followed as follows:

* Annually, when EUS and/or MR imaging detect:  
  - No pancreatic abnormalities  
  - Small cystic lesions morphologically compatible with simple cysts (<10 mm)
* Adjustment of the screening interval to:  
  - 3 months in case of the detection of a hypodense lesion of unknown clinical significance  
  - 6 months in case of a newly detected cyst or branch duct-IPMN with a diameter >10 mm and <30 mm without malignant features (see below)
* In case of the detection of one of the below-listed lesions, the patient will be discussed in an expert panel and/or referred to a pancreatic surgeon:  
  - Solid lesion that is morphological suspicious for a malignancy  
  - Cystic lesion >30 mm  
  - Cystic lesion with malignant features (intracystic nodules, irregular thickened cyst wall, paracystic mass)  
  - Main-duct IPMN  
  - Significant change in size and morphology of existing lesion during follow-up

### **Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. There are no specific criteria for withdrawal applicable for this study.

### **Replacement of individual subjects after withdrawal**

Not applicable for this study.

### **Follow-up of subjects withdrawn from treatment**

If a subject decides to withdraw from the study, informed consent will be asked to interview them by phone on yearly basis. The aim of this yearly interview is to assess information about relevant clinical events that might have developed within their personal medical history or their family medical history.

### **Premature termination of the study**

Not applicable for this study.

1. SAFETY REPORTING

### **AEs, SAEs, and SUSARs**

#### **Adverse events (AEs)**

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the diagnostic procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

#### **Serious adverse events (SAEs)**

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

* Results in death
* Is life threatening (at the time of the event)
* Requires hospitalization or prolongation of existing inpatients’ hospitalization
* 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 to the accredited Institutional Review Board 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.

#### **Suspected unexpected serious adverse reactions (SUSARs)**

Not applicable for this study.

### **Annual safety report**

Not applicable for this study.

### **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.

### **Data safety monitoring board (DSMB) / Safety committee**

Not applicable for this study.

1. STATISTICAL ANALYSIS

### **Descriptive statistics**

Depending on distributional properties of the outcome measures, data will be expressed as means ± the standard deviation (SD) or as medians with range. Statistical significance will be assessed using the Student’s t-test for normally distributed, continuous data, the Chi-square test, and the Wilcoxon test for non-parametric data. A two-tailed *p* value of < 0.05 will be considered significant. The κ coefficient, Spearman correlation coefficient and Lin’s concordance correlation coefficient will be used to analyze the agreement in imaging test results for categorical and continuous variables (presence or absence of lesion(s), size, location and total number of lesions).

### **Univariate and multivariate analysis**

Univariate and multivariate linear and/or logistic regression analyses will be used to evaluate possible and independent factors associated with pancreatic lesions.

### **Interim analysis**

Not applicable for this study.

1. ETHICAL CONSIDERATIONS

### **Regulation statement**

This study will be conducted according to the principles of the Declaration of Helsinki (sixth version, 2008) and in accordance with <SPECIFY NATIONAL REGULATORY LAW>.

### **Recruitment and consent**

The recruitment of high-risk individuals is derived from different sources:

* Clinical geneticist: Patients with a family history of pancreatic cancer and/or carriers of a pancreatic cancer prone gene mutation who have sought consultation with a clinical geneticist can be referred for surveillance for pancreatic cancer.
* Medical specialists who are responsible for the clinical care of patients with pancreatic cancer, including gastroenterologists, internists and surgeons: In case of a candidate family with presumed increased risk for developing pancreatic cancer, this family can be referred to our study group, after which a consultation with the clinical geneticist can be arranged.
* General practitioners: Potential study candidates can be referred by general practitioners to the study group, after which a consultation with the clinical geneticist can be arranged.

As stated in the methods section, all potential new inclusions will be extensively evaluated before inclusion (either by the clinical geneticist or the investigator). Individuals with an estimated ≥ 10-fold increased risk are informed about the pancreatic surveillance study. The aims, methods, anticipated benefits, and potential hazards of the study are explained. This information is also provided in print. Subsequently, the patient 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 also consult an independent physician.

### **Objection by minors or incapacitated subjects**

Not applicable for this study.

### **Benefits and risks assessment, group relatedness**

* Benefits: (1) early disease detection and thereby reduction of pancreatic cancer related mortality, gains in life years and preventing people from dying of pancreatic cancer.
* Risk: (1) complications directly related to the screening procedure (EUS/MRI), (2) screening related drawbacks being over-diagnoses, false positive test results, and false negative test results (3) surgical complications.
* Group-relatedness: not applicable.

### **Compensation for injury**

<INSTITUTION DEPENDENT>

### **Incentives**

Not applicable for this study.

1. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### **Handling and storage of data and documents**

Collected data will be recorded in an online international registry (eCRF). The local principal investigator remains owner of the data. The local principal investigator or delegated co-investigator is responsible for the data entry. All data will be de-identified, the date of birth and a generated individual subject-number will identify patients in the eCRF. Only the local clinical site will have the identifying information for the patient. The principal investigator is able to authorize access to the eCRF for investigators and/or treating physicians for the purpose of research or clinical care.  
  
The informed consent form will also be stored digitally within the eCRF. A paper copy of the informed consent form can be stored locally.

### **Monitoring and Quality Assurance**

<INSTITUTION DEPENDENT>

### **Amendments**

Amendments are changes made to the research after a favourable opinion by the IRB has been given. All amendments will be notified to the IRB that gave a favourable opinion.

### **Annual progress report**

The sponsor/investigator will submit a summary of the progress of the trial to the IRB 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.

### **Temporary halt and (prematurely) end of study report**

The investigator will notify the IRB of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the investigator will notify the IRB, 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 IRB.

### **Public disclosure and publication policy**

<INSTITUTION DEPENDENT>

1. STRUCTURED RISK ANALYSIS

Not applicable for this study.

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