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 15 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.