UniversitätsKlinikum Heidelberg

ChroPac

Duodenum-preserving head resection versus pancreatico-duodenectomy for chronic pancreatitis of the head.

KKS Heidelberg

Organization

- **Trial Coordination**:
  - The Study Centre of the German Surgical Society (SDGC) Heidelberg
  - Prof. Dr. C. Seiler, Dr. A. Moreno-Borchart, I. Rossion, S. Kunz
- **Biometrician / Data Management**:
  - Institute of Medical Biometry and Informatics (IMBI)
  - Dr. T. Bruckner, K. Pieper
- **Clinical Monitoring**:
  - Coordination Centre for Clinical Trials (KKS) Heidelberg
  - D. Jackson, M. Diallo, A. Freiberger (Projekt Controller)

General Trial Information

- Trial Design:
  Randomized, controlled, observer and patient blind, multi-centre with 2 parallel study groups

- Objective:
  investigate differences in QoL after surgery

General Trial Information

- Indication: primary operation for pancreatitis of the pancreatic head
- Patients: 200
- Recruitment: 24 months
- Follow up: after 6, 12 and 24 months
- Centre: 13 (11 national, 2 international)
  - about 15 patients per Centre

Timelines

- First patient in: June 2009
- Last patient out: May 2013
- Initial Report: 4 Quarter 2013

Treatment

Arm A:

Any surgical technique that removes inflamed pancreatic tissue of the head without resection of the duodenum e.g.

- Beger
- Frey
- Berne

Arm B:

- Pancreatico-duodenectomy
  - Pylorus preserving
  - classic Whipple

Primary Objective and Endpoint

Average Quality of Life measured 6, 12 and 24 months after surgery by the EORTC QLQ-C30 scale

Secondary Objectives and Endpoints I

- Mortality
- Morbidity
  - Wound infection
  - Pulmonary infection
  - Pancreatic fistula
  - Delayed gastric emptying
- EORTC QLQ-C30 and PAN 26 sub scores
- Total hospital stay due to chronic pancreatitis within 24 months after randomization

Secondary Objectives and Endpoints II

- Reoperation due to recurrence of chronic pancreatitis
- Weight gain
- New onset of diabetes mellitus requiring treatment
- Development of exocrine insufficiency
- Operation time
- Blood loss assessed by surgeons and anesthetists

Inclusion Criteria

- Patients with chronic pancreatitis of the head and pain eligible for primary elective surgery
- Ability of subject to understand character and individual consequences of the clinical trial
- Written informed consent

Exclusion Criteria

- Participation in another intervention-trial with possible interference of intervention and outcome of this study

Informed Consent

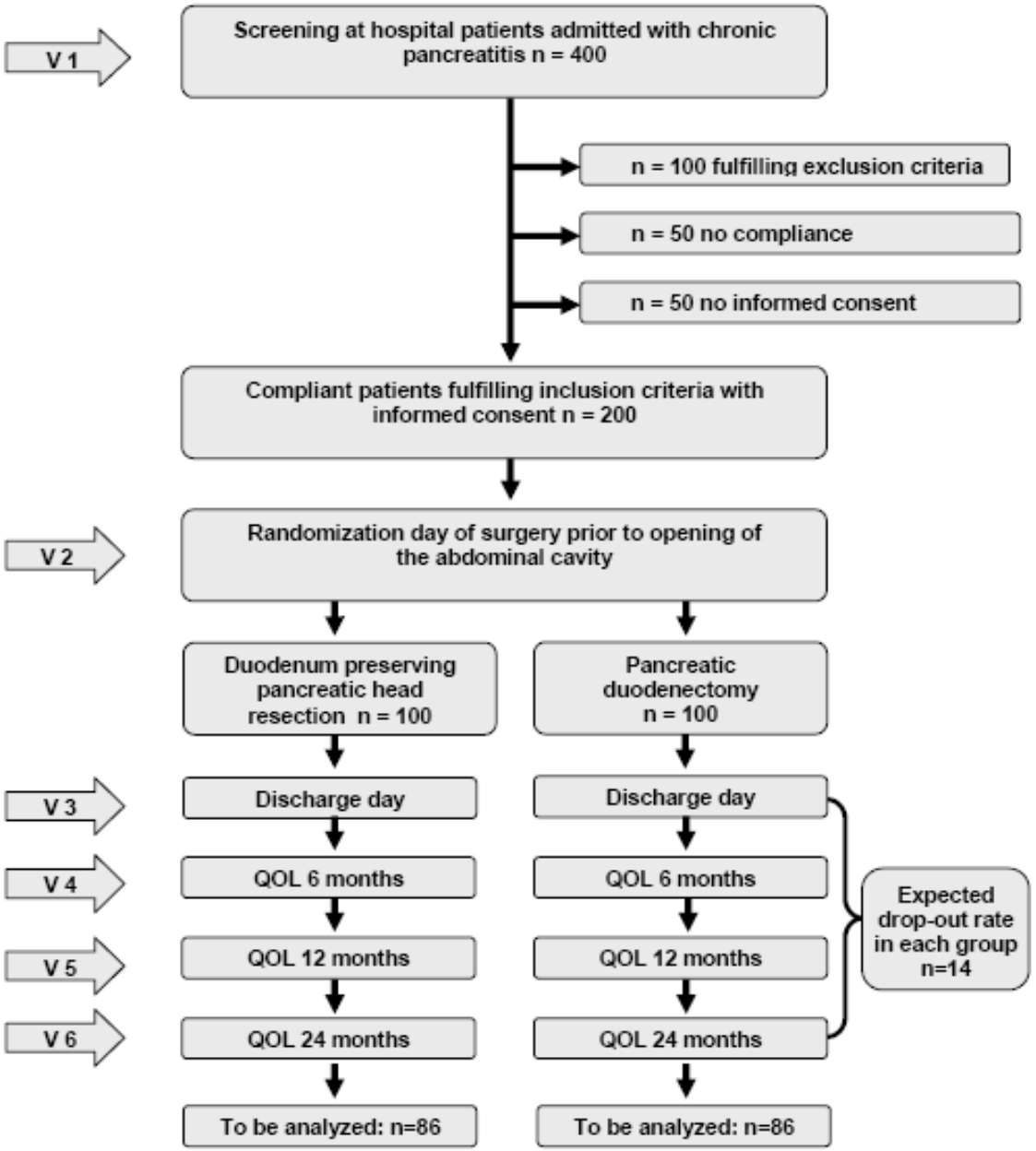
- Signed and dated by patient
- While Doctor present
- Copy for patient / Original in Investigator Study File (ISF)
- Explain that patient can withdraw at any time without giving reason for their decision

Blinding

- Patient and Outcome Assessor blind
- Operation details are to be stated in surgical report only.
- In the Physician‘s letter there is to be no mention of what type of operation the patient has undergone.

Examples of blinding in Physician Letter

- Resection of the pancreatic head
- “Patients name” is participating in a clinical trial „ChroPac“; the objective of the trial is to investigate duodenum-preserving pancreatic head resection versus pancreatico-duodenectomy
- Since “patients name” is participating in the ChroPac trial he/she does not know what exact procedure was done. If patient would like to know the information will be given to him/her.


V 1
Screening at hospital patients admitted with chronic pancreatitis n = 400
n = 100 fulfilling exclusion criteria
n = 50 no compliance
n = 50 no informed consent
Compliant patients fulfilling inclusion criteria with informed consent n = 200
V 2
Randomization day of surgery prior to opening of the abdominal cavity
Duodenum preserving pancreatic head resection n = 100
Pancreatic duodenectomy n = 100
V 3
Discharge day
Discharge day
V 4
QOL 6 months
QOL 6 months
V 5
QOL 12 months
QOL 12 months
V 6
QOL 24 months
QOL 24 months
Expected drop-out rate in each group n=14
To be analyzed: n=86
To be analyzed: n=86

Visit 1: Screening

- In-/Exclusion Criteria
- Quality of Life (patient must complete independently)
- Demography
- Duration of chronic pancreatitis related symptoms
- Imaging
- Results of Preoperative Endoscopy
- Total number of ERCPs

Visit 2: Operation

- Randomization
- Intraoperative confirmation of Indication
- Operation Time (first incision, closure)
- Performed Surgical Resection
- Blood Loss (assessed by surgeon and anesthetist)
- SAEs
- Translational Research Samples

Visit 2: Operation

- According to local standards
- If patient is randomized in Whipple Arm it is up to the surgeon to remove pylorus or not

Visit 3: Discharge

- Date of Discharge
- Final Histological Examination
- Study-Related Examination (Secondary Endpoints)
  - Wound infection
  - Pulmonary infection
  - Pancreatic fistula
  - Delayed gastric emptying
  - Weight
  - Diabetes mellitus
  - Exocrine insufficiency (continuous supplement of enzymes)
  - SAEs

Visit 4: 6 +/- 1 Months

- Quality of Life (QLQ-C30 / PAN 26)
- Study-Related Examination
  - Wound infection
  - Pulmonary infection
  - Pancreatic fistula
  - Hospital stay due to chronic pancreatitis
  - Reoperation due to recurrence of chronic pancreatitis
  - Weight
  - Diabetes mellitus
  - Exocrine insufficiency (continuous supplement of enzymes)
  - SAEs

Visit 5: 12 +/- 1 Months

- Quality of Life (QLQ-C30 / PAN 26)
- Study-Related Examination
  - Hospital stay due to chronic pancreatitis
  - Reoperation due to recurrence of chronic pancreatitis
  - Weight
  - Diabetes mellitus
  - Exocrine insufficiency (continuous supplement of enzymes)
  - SAE's

Visit 6: 24 +/- 1 Months

- Quality of Life (QLQ-C30 / PAN 26)
- Study-Related Examination
  - Hospital stay due to chronic pancreatitis
  - Reoperation due to recurrence of chronic pancreatitis
  - Weight
  - Diabetes mellitus
  - Exocrine insufficiency (continuous supplement of enzymes)
  - SAE's

Randomization I

- Randomization day of surgery
- https://www.randomizer.at/random
- Screening Number: 3-digit, beginning with 001
- Pat. Screening-Number to be used as Pat.-Number
- The randomization number will be given by Randomizer.at

Randomization II

- Requirement for every user:
  1. Registration ⇒ Password (see Instructions ISF chapter 3.3)
  2. Account activation

➔Passwords cannot be shared!!!

Randomization III

- „How to randomize“
- Test version: https://www.randomizer.at/demo

Randomization IV

Attention:

The accounts for the Randomizer.at will not be activated until the site has be initiated and all essential documents have been collected.

Adverse Events (AE)

Only the secondary Endpoints will be assessed as adverse events

(only documented during the follow up visits)

- Pulmonary infection
- Wound infection
- Pancreatic fistula
- Delayed gastric emptying
- Hospital stay due to chronic pancreatitis
- Reoperation due to recurrence of chronic pancreatitis
- Diabetes mellitus
- Exocrine insufficiency (continuous supplement of enzymes)

Serious Adverse Events (SAEs)

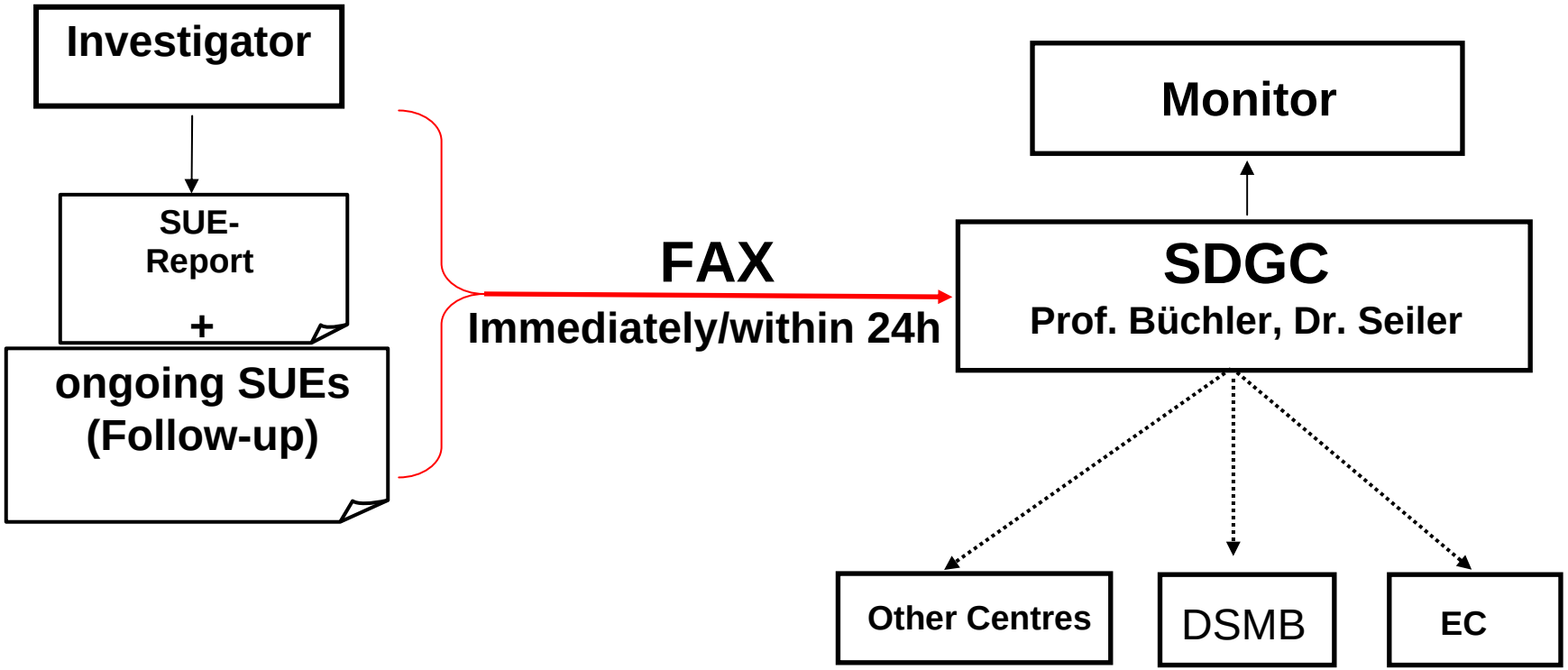
A serious adverse event is an event, that:

- Results in death
- Is immediately life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity

SAE Exceptions

- delayed gastric emptying
- new onset of diabetes mellitus
- development of exocrine insuffiency
- Reoperation due to chronic Pancreatitis

SAE-Reporting



SAE-Reporting

- SAE-Reporting Form
- Fax numbers:

  ++49 / (0)6221/ 56-33850 (SDGC)

  ++49 / (0)6221/ 56-33508 (Monitor)

Criteria for Withdrawal

- At their own / legal representative request
- If, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being

Monitoring I

- Support and surveillance of clinical trials to insure quality assurance
- Monitoring procedures will be adapted to:

  - study specific risk for patients

  - interpretation of ICH-GCP

  - standard operating procedures (SOP) of the KKS

to ensure patients safety and integrity of the clinical data

Monitoring II

Frequency:

- First Monitoring visit: Shortly after the fist patient has been randomized
- Following Monitor visits: about 3 Visits

Monitor visit:

- Verification of completeness of contents
- Source Data Verification
- Inspection of CRFs (correctness, completeness and protocol compliance)
- Verification that all SAEs were / are reported

Source Documents

for example:

- Informed Consent, Demography, OP-Report, Lab results, Imaging results, AEs, Medical History...

- All source documents have to be present during the Monitor visit

Investigator Study File (ISF)

Store away from unauthorized individuals (in locked cabinet/room)

Lists to maintain:

- Log of Staff
- Subject Identification List
- Screening / Randomization Log

Queries

- Queries (Data Clarification Forms):
  - sent directly to the centre
  - resolved queries are to be sent directly back to Data Management
  - file a copy in the ISF under 10.2

Translational Research (day of operation)

Blood collection

- 2x Serum S-Monovettes each 9 ml
- Vein puncture preoperatively between 7 and 9am
- Preperation (s. instructions); store at -20°C

Translational Research

Tissue samples (3 x max.5 mm²)

- First part:

→ snap-frozen, then storage in -80°C freezer

- Second part:

→ 12-24 hr. in Histoformalin, then storage in Ethanol at room temperature

- Third part:

→ in RNAlater (store overnight at 4°C, then transfer to -80°C freezer

Thank you for your attention

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