Distal Pancreatectomy
A randomized controlled trial to compare two different surgical techniques

DISPACT-TRIAL
ISRCTN 18452029

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1 GENERAL INFORMATION

1.1 Title of the Trial
Distal Pancreatectomy – A randomized controlled trial to compare two different surgical techniques - DISPACT-TRIAL.

1.2 Coordinating / Principle investigator
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1.3 Scientific discipline and field of work
The DISPACT-TRIAL is a project of the Study Center of the German Surgical Society (SDGC), Heidelberg, Germany. The topic of this trial refers to the field of visceral surgery.

1.4 Scheduled duration
The projected start and inclusion of the first patient is May 1st 2006. Thenceforward, the scheduled duration is planned to be 54 months from start of recruitment to the reporting of the final results. The total duration of the trial results from a scheduled recruitment time of 36 months and a consecutive 12 month follow up. Three months after completion of follow up the database will be closed with a consecutive final analysis (three months).

1.5 Staff and institution’s contribution
This multi-center trial is supported by the Study Centre of the German Surgical Society (SDGC).
1.6 Funding

**Protocol development**
University of Heidelberg, Medical School
Heidelberg, Germany

**Trial implementation, personal, management and infrastructure**
Study Centre of the German Surgical Society (SDGC)
University of Heidelberg
Im Neuenheimer Feld 110
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**Surgical material**
Study Material (staplers and suture material) will be supplied by ETHICON™. The company neither had influence on the protocol development nor will have on the conduct and analysis of the trial results.

1.7 Registration
Registration of the trial will be processed immediately upon receipt of a positive vote of the local independent ethics committee to receive an International Standard Randomised Controlled Trial Number (ISRCTN; www.controlled-trials.com).
The assigned ISRCTN number from the Current Controlled Trials register is as followed: **ISRCTN 18452029.**
1.8  Investigators, Sponsor, Biometrician and monitor

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<td><strong>Bochum:</strong></td>
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<td>Prof. Dr. W. Uhl</td>
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<td><strong>Ulm:</strong></td>
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<th><strong>Monitoring</strong></th>
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<tbody>
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<th><strong>Sponsor</strong></th>
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<td><strong>Principal Sponsor</strong></td>
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<td><strong>Trial implementation, personal, management, analysis and infrastructure:</strong></td>
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<td>Federal Ministry for Education and Research (BMBF)</td>
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| **General Contact / Information** |  |
1.9 Overview – trial design and implementation

Population: Hospitalized patients, planned for elective resection of the pancreatic tail due to chronic pancreatitis, benign tumors, malignant tumors, neuroendocrine tumors and cysts.

Screening day of admission:
- Inclusion/exclusion criteria
  - Not eligible
  - Refuse participation
  - Eligible
    - Informed consent/enrolment
      - Randomization (preop.)
        - Stapling vs. hand-sewn closure
          - Primary and secondary endpoints
            - Primary and secondary endpoints
              - Primary and secondary endpoints
                - Survival
### 1.10 Flowchart

#### Course of examinations

<table>
<thead>
<tr>
<th>Visit</th>
<th>1 (=Screening)</th>
<th>2 (OP =day0)</th>
<th>3 (day 7 post OP)</th>
<th>4 (day of discharge)</th>
<th>5 (day 30 post OP) by phone</th>
<th>6 (12 months post OP) by phone</th>
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<tr>
<td>Past and current medical history</td>
<td>X</td>
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<tr>
<td>Informed consent</td>
<td>X</td>
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<tr>
<td>Physical examination / personal data</td>
<td>X</td>
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<td></td>
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<tr>
<td>Basic study-related examination (for each primary and secondary endpoint,)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>AE, SAE</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Grade of fibrosis</td>
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<td>Drainage parameters</td>
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<td>Laboratory parameters</td>
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<td>Endocrine function</td>
<td>X</td>
<td>X</td>
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<td>Survival</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
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Past and current medical history: past and current medical and surgical history, indication for operation
Personal data: height in cm, weight in kg, age, gender, smoking habits
Basic study related examination: physical examination for each secondary endpoint or adverse event/serious adverse event
Physical examination: vital signs (blood pressure systolic/diastolic in mmHg, heart rate in /min)
Grade of fibrosis: measured by central laboratory of the European Pancreatic Center (EPZ), Dept. of Surgery, University of Heidelberg
Laboratory parameters: serum chemistry, clotting, hematology, endocrinology
Drainage parameters: Amylase activity in drain fluid output, clinical grading
Endocrine function: Serum glucose level
Visit 5: by phone; performed by participating centers
Visit 6: by phone; performed by participating centers
In case of an extra visit performed by the investigator primary and/or secondary outcomes may be reached, AE/SAE form may be necessary.
## 1.11 Summary

<table>
<thead>
<tr>
<th>Title of trial</th>
<th>Distal Pancreatectomy – A randomized controlled trial to compare two different surgical techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Acronym)</td>
<td>DISPACT-TRIAL</td>
</tr>
<tr>
<td>Disease or condition</td>
<td>Patients with diseases of the pancreatic body and tail undergoing elective distal pancreatectomy due to: resectable malignant, non-malignant and neuroendocrine tumours of the pancreas (high risk level), resectable chronic pancreatitis and pseudocysts (low risk level).</td>
</tr>
<tr>
<td>Design / methodology</td>
<td>This is a multi-center, pre-operatively randomized, controlled and patient and observer blinded trial performed as a parallel group adaptive superiority design. The randomization is done stratified for centers and risk level (low/high). The patient is blinded for the technique used in order to prevent an impact on secondary endpoints.</td>
</tr>
<tr>
<td>Topic / objectives / aim</td>
<td>The trial is designed to show that the risk of developing a pancreatic fistula and/or death until day 7 after the surgical procedure can be reduced by stapler-closure of the pancreatic remnant compared to scalpel transection and hand-sewn suture following distal pancreatectomy.</td>
</tr>
</tbody>
</table>
| Eligibility criteria - inclusion | • Age equal or above 18 years  
• Expected survival time more than 12 months  
• Patients with at least one of the following pathologic diseases scheduled for elective resection:  
  - Resectable malignancies of the pancreatic body and/or tail  
  - Resectable chronic pancreatitis of the body and/or tail  
  - Resectable benign tumours of the pancreas including neuroendocrine tumours  
  - Resectable pseudocyst of the pancreatic body and/or tail |
| Eligibility criteria - exclusion | • Current immunosuppressive therapy  
• Chemotherapy within 2 weeks before operation  
• Radiotherapy within 8 weeks before operation  
• Curative resection is not feasible  
• Severe psychiatric or neurologic diseases  
• Drug- and/or alcohol-abuse according to local standards  
• Participation in another intervention-trial with interference of intervention or outcome  
• Inability to follow the instructions given by the investigator or interviewer  
• Expected lack of compliance  
• Lack of informed consent |
| Groups / interventions | A standardized surgical abdominal approach is performed in both groups with a stapler-resection / -closure versus scalpel transection and hand-sewn closure of the pancreatic tail. |
| Endpoints / primary outcome(s) | Combined primary endpoint: presence of a pancreatic fistula and / or death due to any cause on day 7 postoperatively.  
Secondary endpoints: operating time, frequencies of burst abdomen, wound infection, and intraabdominal fluid collection and abscess, postoperative length of hospital stay, new onset of diabetes mellitus, one-year survival. |
| Sample size | A total of approximately 550 patients may be included with an expected pre-operative drop out rate of 100 patients. Thus, 450 patients will be randomized to accumulate 151 patients in both groups respectively for analyses (assumed protocol violations / lost to follow-up per group: 74 patients) The sample size will be recalculated after an interim analysis when 112 patients per arm are evaluable. |
| Trial duration | • Duration of enrolment: 36 months  
• Interim analysis: after about 29 months  
• Duration of treatment: Day of Surgery  
• Duration of follow-up: 1 month for adverse events  
  12 months for survival  
• End of follow-up period: 12 months after recruitment of the last patient  
• Duration of analysis and reporting: The database will be closed 6 months after the end of follow up. Evaluations and reporting will be finished 6 months thereafter. |
Abbreviations and definitions

CRF    Case Report Form

eCRF  electronic Case Report Form

GCP    Good Clinical Practice

ICH    International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IRB    Institutional Review Board

RCT    Randomized controlled trial

SDGC  Study Center of the German Surgical Society (Studienzentrum der Deutschen Gesellschaft für Chirurgie)

KKS    Coordinating Center for Clinical Trials (Koordinierungszentren für Klinische Studien)

IMBI   Institute for Medical Biometrics and Informatics

(Institut für Medizinische Biometrie und Informatik)

EPZ    European Pancreas Centre (Europäisches Pankreas Zentrum)

CI     Confidence interval

OR     Odds ratio

DSMB   Date Safety and Monitoring Board

ARR    Absolute Risk Reduction

RRR    Relative Risk Reduction

SOC    System Organ Class.
2 The medical problem

2.1 Evidence

After distal pancreatectomy, the appropriate closure of the remnant is still debated. All resections of this endocrine organ to the left side of the superior mesenteric vein are defined as distal pancreatectomy. Distal pancreatic resections are performed less frequently (15% of all pancreatic resections in Heidelberg) compared to resections of the head due to lower incidence and later appearance of clinical symptoms. Nevertheless, the improving imaging and diagnostic techniques account for an increase in frequency of distal pancreatic resections due to pancreatic disease. Most patients (84%) are treated as elective cases for the following indications: chronic pancreatitis (24%), other benign diseases (22%), malignant diseases (18%), neuroendocrine tumours (14%), and cysts of the pancreas (6%). The remaining 16% are emergency cases after abdominal trauma.

In the past years, mortality after pancreatic resections has decreased considerably in high volume centers, with still a high morbidity. Pancreatic fistula and leakage are the most common and most relevant complications due to surgical technique and skill.

The major complication after distal pancreatectomy is the occurrence of a pancreatic fistula. Since fistulae are associated with local and general complications (pancreatic fluid collection, formation of intra-abdominal abscesses, wound infection, delayed gastric emptying, respiratory complications, sepsis and bleeding), they have several relevant implications for the patient, the surgeon and the health care system. This morbidity causes a prolongation of hospital stay due to the additional need for specialised treatment including invasive procedures such as additional surgery or interventional drainage.

A recent systematic review and meta-analysis evaluated all available surgical techniques of distal pancreatectomy, in particular with regard to the occurrence of pancreatic fistulae: hand-sewn suture techniques versus stapled closure and combination of both, ultrasonic dissection devices, pancreatico-enteric anastomosis, application of meshes, or sealing by use of fibrin glue. As expected, stapler-closure and hand-sewn closure of the pancreas were found to be the most common techniques.

The reported postoperative morbidity varies between 13.2% and 64%. The primary outcome measure, pancreatic fistula, occurred within a range from 0% - 61%. Meta-analysis of stapler versus hand-sutured closure (one RCT; five observational studies) showed a non-significant (P = 0.21) combined odds ratio for the occurrence of a pancreatic fistula of 0.66 (95% confidence interval 0.35 to 1.26) in favour of stapler-closure (Fig. 1).
2.2 The need for a trial
Given the results of the systematic review, the quality and quantity of information extracted from the trials performed are still insufficient to draw any firm conclusions on the optimal choice of surgical technique to close the pancreatic stump.

To prove the appropriateness of stapler-transsection and –closure of the pancreatic remnant as a standard will influence the future surgical techniques in distal pancreatectomy and general health care. This technique has to be compared with the reference treatment of the hand-sewn closure of the pancreatic tail. In order to generate unbiased and valid data and due to rare pancreatic left resections, this question has to be answered in a prospective, randomized-controlled multi-center trial using the frequency of pancreatic fistula and/or mortality as primary endpoint.

Figure 1: Meta-analysis of closure techniques in distal pancreatectomy (Stapler-closure vs. Suture-closure) 11.

The odds ratio estimates of occurrence of a pancreatic fistula for individual trials are shown in boxes calculated by the random effects model. Error bars indicate 95% CI. Summary of treatment effect is shown as a diamond that spans the 95% CI.

Quality: Allocation concealment – adequate (A); unclear (B); inadequate (C); not used (D)

2.3 Aim of the Trial
A successfully conducted trial will have a positive impact on the future handling of the pancreatic remnant in distal pancreatectomy. The reliable and comparable data generated in this trial may support an evidence-based choice of a surgical technique out of a wide range of existing techniques. The reduction of the fistula rate, as the major complication of distal pancreatectomy, may lead to a decrease in further associated complications. In particular, the length of hospital stay and additional interventional procedures can be reduced and a return to full recovery will be accelerated. Additionally, costs of the post-operative treatment may be reduced as to the impact on the health care system. Moreover, this multi-center approach may
show that the introduced technique is appropriate for different settings and therefore shall be transferable to other health care institutions.

After analysis and statistical evaluation, results will be published in a scientific medical journal. Publication of the trial protocol is in preparation.
3 Trial Design

3.1 Trial population
Hospitalized patients with pancreatic disease, planned for an elective pancreatic tail resection.

3.2 Primary objective
The trial is designed to show that the risk of developing a pancreatic fistula and/or death after the surgical procedure can be reduced by stapler-closure of the pancreatic remnant compared to scalpel transsection and hand-sewn suture following distal pancreatectomy.

3.3 Secondary objective
Besides the occurrence of a pancreatic fistula and/or death due to any cause a set of general and surgical parameters have to be analyzed in order to compare the two surgical approaches. In order to compare the effectiveness of both procedures adequately, relevant parameters of postoperative mortality and morbidity and survival will be analyzed (see 3.9).

3.4 Hypothesis
The trial is designed to show that the risk of developing a pancreatic fistula and/or death after the surgical procedure can be reduced by stapler-closure compared to scalpel transsection and hand-sutured closure of the pancreatic remnant following distal pancreatectomy. The following hypothesis will be tested:

\( H_0: \) The risk of morbidity (pancreatic fistula) combined with mortality is equal in both groups.

\( H_1: \) The risk of morbidity (pancreatic fistula) combined with mortality is different between both groups.

3.5 Selection and withdrawal of patients
3.5.1 Inclusion/Exclusion criteria
Subject inclusion criteria
- Age equal or above 18 years
- Expected survival time more than 12 months
- Patients with at least one of the following pathologic diseases scheduled for elective resection:
- Resectable malignancies of the pancreatic body and/or tail (e.g. all tumor that can be safely taken out after exploration (including splenectomy and other visceral organ removal), i.e. a potentially curative resection)
- Resectable chronic pancreatitis of the pancreatic body and/or tail
- Resectable benign tumours of the pancreatic body and/or tail including neuroendocrine tumours
- Resectable pseudocysts pancreatic body and/or tail

**Subject exclusion criteria**

- Current immunosuppressive therapy (more than 40 mg of a corticoid per day or azathioprin)
- Chemotherapy within 2 weeks before operation
- Radiotherapy within 8 weeks before operation
- Curative resection is not feasible (e.g. palliative situation of disease)
- Severe psychiatric or neurologic diseases
- Drug- and/or alcohol-abuse according to local standards
- Participation in another intervention-trial with interference of intervention or outcome
- Inability to follow the instructions given by the investigator or the telephone interviewer (insufficient command of language, dementia, lack of time)
- Expected lack of compliance
- Lack of informed consent

3.5.2 Subject withdrawal criteria

Subjects may be withdrawn from the trial for the following reasons:

- Own request of the patient or at the request of their legally authorized representative
- Causes detrimental to the subject's well-being in the investigators opinion
- Non-resectable situation after the exploration of the abdomen.

The documentation of withdrawal will be done on a separate screening list of all patients.

3.6 Criteria for the selection of trial sites

It is planned to include up to 20 highly specialized centers (performing at least 10 left resections of the pancreas/year) in Germany and other European countries. The participating centers will be checked for their expertise, particularly in distal pancreatectomy, prior to their enclosure. Moreover, the installation of a client-software (CITRIX) should be possible in order to assure access to eCRFs.
An initiation visit is planned to introduce the background, rationale and implementation of DISPACT-Trial in every single participating centre.

3.7 Primary and secondary endpoints

Combined primary endpoint:
- Occurrence of a pancreatic fistula (specification see 3.10.1.1).
- Death due to any cause until the postoperative day 7 (specification see 3.10.1.1).

Secondary endpoints:
Aside from the occurrence of a pancreatic fistula, several parameters have to be analyzed in order to compare the two surgical approaches. The following secondary endpoints include general and specific surgical adverse events as well as parameters concerning the intraoperative and postoperative course of a patient (specification see 3.10.1.2).

1. Surgical category
- Operating time [min] from resection to beginning of closure of the abdomen
- Total operating time [min]
- Frequency of burst abdomen
- Frequency of wound infection
- Frequency of intra-abdominal fluid collection rated as abscess that requires an intervention (surgery, drainage, antibiotic treatment)

2. Non-surgical category
- Postoperative length of hospital stay
- Frequency of new onset diabetes mellitus (necessity of new anti-diabetic drug treatment)
  - One-year survival

3.8 Methods against bias
Several appropriate methods will be used to minimize bias. Randomization to one of the treatment groups by a central randomization system will generate comparable treatment groups by minimizing selection bias. Stratification for the participating centers will reduce bias by center effects. Stratification for the risk level (low/high) will differentiate patients with high risk (all tumors) and low risk (chronic pancreatitis) for development of a pancreatic fistula. The confirmatory analysis of the primary endpoint will be done stratified for the surgical expertise, to avoid a possible confounding effect.
All surgical procedures are easily applicable and well defined in detailed manuals. Equal treatment according to the specifications in the manual will reduce intra- and intervariability in pancreatic left resection. The investigation of the primary endpoint is based on objective measurements, which are exactly defined. Moreover, only centers that prove to be highly specialized for pancreatic resections (with at least 10 left resections of the pancreas per year) will be included in the trial.

3.8.1 Randomization
A central randomization and registration system (www.randomizer.at) will be arranged in order to generate sufficient allocation concealment. Patients are randomized using the central randomization system before the surgical intervention is performed (at the latest before surgical skin incision).

3.8.2 Stratification
The randomization is done stratified for participating centers and risk level (low/high). Further stratification is planned for up to 20 participating highly specialized centers with at least 10 left resections of the pancreas per year.

3.8.3 Blinding
The patient and the outcome assessor are blinded for the technique used. Thus, outcome assessment during all study visits has to be performed by a blinded clinical investigator and/or study nurse. Moreover, it is recommended to use the phrase “resection in terms of distal pancreatectomy is performed according to randomization in the DISPACT-Trial” in the operating report of enrolled and participating patients to maintain the blinding.

3.8.4 Confounding
Moreover, the confirmatory analysis and reporting of primary and secondary endpoints will be grouped for the following parameters:
Surgeon’s expertise:
- Low surgical expertise: \( \leq 25 \) performed pancreatic resections during the last three years
- Medium surgical expertise: 26 – 50 performed pancreatic resections during the last three years
- High surgical expertise: >50 pancreatic resection during the last three years
The number of previous operations (outside DISPACT-Trial) will be recorded for each surgeon. Thus a surgeon will not change the expertise group during the trial.

3.9 Trial Interventions
Manuals of all surgical procedures will be provided for all participating centers (see 9.9)

3.9.1 Preoperative course
Randomization:
Patients will be randomized preoperatively to one of the following surgical procedures:
1. Scalpel transsection of the pancreas and hand-sewn closure of the pancreatic remnant
2. Stapler-transsection of the pancreas and stapler-closure of the pancreatic remnant
Randomization will be carried out preoperatively at the latest before surgical skin incision. Thus, preoperative randomization is considered to be adequate to control for selection bias.

3.9.2 Intraoperative course
Standardized surgical abdominal approach:
Abdominal approach can be achieved via median or transverse laparotomy according to local standards. A complete exploration of the abdomen is done including frozen sections to define potentially curative resection if necessary. The decision of splenectomy in addition to the planned/performed distal pancreatectomy will be made by the surgeon in accordance with the underlying disease of the patient and the curative intention.

Scalpel transsection and hand-sewn closure of the pancreatic remnant:
After complete mobilization of the pancreatic tail (up to the region of the superior mesenteric vein or at least 2-3 cms central of the planned resection margin), the resection is performed with a surgical scalpel. The subsequent closure of the pancreatic remnant is achieved with a separate stitched ligation of the pancreatic duct, followed by either a single-stitched or running suture closing of the entire pancreatic remnant. The suture material of choice should be a slowly absorbable monofilament thread, such as PDS™ or MonoPlus™. A non-absorbable suture is neither required nor permitted for the hand-sewn closure of the transected pancreas. The recommended suture strength is USP 4/0 and USP 5/0. No additional covering of the pancreatic remnant (e.g. Tachosil™) is permitted in this group.

Stapler-closure:
In the other group the mobilization of the pancreas is performed accordingly (up to the region of the superior mesenteric vein or at least 2-3 cms central of the planned resection margin). The
consecutive pancreatic resection and thus the transection of the pancreatic body will be executed using a linear stapling device (Ethicon TL 60 1.0 – 2.5 mm) armed with a 60mm magazine. The depth of the individual staple can be customized (1.0 mm – 2.5 mm). No additional covering or suturing of the pancreatic remnant is permitted in this group. However, in case of bleeding from the pancreatic remnant or stapler line, single stitches are allowed for hemostasis. Thus, additional complete suturing of the pancreatic remnant in case of stapler-closure has to be omitted.

Since the recording of the amylase levels as well as drain output seem to be an indicator for the assessment of the primary endpoint, each patient must receive at least one intra-abdominal drainage that should be in place until day three after the surgical intervention. The drainage used should comply with local standards. However, the use of a soft, non-rigid drainage (e.g. easy flow) is recommended.

All study material (stapler and suture material, respectively) will originate from one single batch.

**Intraoperative documentation:**

- **Abdominal incision**
  
The technique of laparotomy has to be specified and documented in the CRF (median-/transverse laparotomy).

- **Photo-documentation:**
  
  In order to confirm performance of the standardized surgical procedure different steps of the operation will be documented using digital photography. A total of three photographs have to taken that will be reviewed by the surgical advisory board to ensure treatment per protocol.

  The following surgical steps will be documented:
  1. Complete exposition of the pancreatic body and tail
  2. Closure phase of the distal pancreas according to randomization
  3. Final operative situs after closure of the pancreatic remnant

3.9.3 Postoperative course

**Histological confirmation:**

A central histological confirmation of the grade of fibrosis will be done by the European Pancreas Centre (EPC), Heidelberg, Germany.

In each patient, a complete cross section of the margin of the resected pancreas is taken for the analysis of the grade of tissue fibrosis. The specimen of the margin is separated into two pieces one of which is immediately preserved in RNA later for RNA analysis, the other in Bouin’s solution (60 ml of saturated picrinic acid and 20 ml of 37% formaldehyde) and paraffinized
thereafter. Serial sections of paraffinized tissues will be stained either with hematoxilin and eosin (HE) or with periodic acid Schiff (PAS)-phosphomolybdic acid (PMA)-Diamine Supra Blue for specific detection of collagen fibers. The quantitative distribution of connective tissue (fibrosis) and parenchyma will be measured with a computer-aided picture-analyzing system (Leitz T.A.S.; Leitz, Wetzlar, Germany).

**Assessment of primary and secondary endpoints**

See section 3.11

**Specification of follow-up visits**

The follow-up visits after hospital discharge (visit 5-6) will be done by telephone interview. This interview will be standardized, as predefined questions have to be answered with YES/NO by the patient. The following items will be the backbone of the telephone interviews on day 30 and 12 months postoperatively:

1. Have you had any pain, discomfort, or other adverse events since your discharge? YES/NO
   a. If YES please specify. TEXT
   b. If AE: find out all AE related information.
2. Have you contacted your GP or any other physician? YES/NO
   a. If YES, were any medical interventions necessary? YES/NO
      i. If YES, please specify. TEXT
   b. If YES, contact details. TEXT
3. Have you been re-admitted to hospital since your discharge? YES/NO
   a. If YES, were any medical interventions necessary? YES/NO
      i. If YES, please specify. TEXT
   b. If YES, contact details. TEXT

Fill out the CRF page "Endpoints" as follows:

- The 1. question serves as an indicator for adverse events.
- If questions 1.-3. were answered with NO: Fistel NO, Burst abdomen NO, Wound infection NO, Intra-abdominal fluid collection and abscesses NO, New onset of diabetes mellitus NO, Any adverse event NO.
- If question 1. answered with YES but 2. and 3. with NO: If the existence of a primary or secondary endpoint is suspicious but medical evaluation has not been done to the
timepoint of the follow-up visit, the responsible on-site investigator has to arrange the necessary investigations / assignments.

- If question 2. or 3. answered with YES: Contact the GP, physician and/or hospital to check for any endpoints.

Investigators will be supported by an information sheet (including a copy of the endpoint page and adverse event page) for the telephone interview with the patients. This sheet is not part of the CRF and remains at the study site and serves as source documentation.

Explanations:
If relevant discomfort, pain, hospital re-admittance, re-intervention and/or re-operation will be negated by the patient, the responsible investigator has to exclude the existence of a pancreatic fistula. Also the existence of secondary endpoints, such as burst abdomen, clinical relevant fluid collections and intra-abdominal abscesses etc. will be evaluated by pre-defined questions. In case of a suspected or proven pancreatic fistula clinical grading of the fistula has to be done by a clinical investigator (physician). Also, the existence of secondary endpoints has to be verified by the necessary documents or investigations (medical reports of examinations or interventions). If the existence of a primary or secondary endpoint is suspicious but medical evaluation has not been done to the timepoint of the follow-up visit, the responsible on-site investigator has to arrange the necessary investigations / assignments.

3.10 Treatments permitted and not permitted
It is not allowed to randomize a patient when the resection will be without curative intention, i.e. all patients with palliative procedures are being excluded from the study. No further suturing of the pancreatic remnant should be done in case of stapling. The only exception is the application of single ligations for hemostatic reasons. The application of octreotide according to local standards (e.g. sandostatin) will be done according to local standards of the centre. However, the use has to be specified in the eCRF. Once randomized, a patient has to be maintained in the study and analysed according to the determined group (Intention-To-Treat principle).

Prior and concomitant illnesses and medication
Prior illnesses of each patient will be documented during the initial screening visit in the CRF on a “concomitant medical conditions” form. Concomitant illnesses during the participation in the trial are comprehended as adverse events.
Aside from octreotid (e.g. Sandostatin®) there no evidence exists concerning a causal relationship of concomitant medication and the incidence of pancreatic fistulae. Therefore, the concomitant medication will not be documented. In contrast, the documentation of the octreotid-application is part of the standardized surgical procedure, which has to be documented in the CRF (see 2.16. 10 standard surgical procedures).

3.11 Specification and assessment of the efficacy parameters

Primary Endpoint:
The primary endpoint is a combination of occurrence of a postoperative pancreatic fistula and/or death due to any cause until postoperative day 7.

Occurrence of a pancreatic fistula is postoperatively assessed by the local study team of the participating center. Pancreatic fistulae after discharge will be detected by the follow-up visits (visit 5-6) until 12 months postoperatively. Intraoperative or postoperative death due to any cause will be assessed until the postoperative day seven.

The definition of pancreatic fistula was elaborated by an international expert group of pancreatic surgeons and was reported in its final version during the European Pancreatic Club, Padova, Italy in June 2004.
Definition of a pancreatic fistula:

1. All-inclusive definition: Drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity.

AND/OR

2. Clinical Grading:
   - Grade A: "Transient fistula" with no clinical impact.
   - Grade B: Requires change in management (e.g. partial or total parenteral nutrition; leukocytosis, interventional drainage, antibiotics, somatostatin analogues, extended hospital stay, readmission)
   - Grade C: Major change in clinical management (e.g. total parenteral nutrition, i.v. antibiotics, somatostatin analogues, sepsis, organ dysfunction, intervention, revision of anastomosis, and delay in hospital discharge)

Definition of death:

Intraoperative or postoperative death due to any cause until postoperative day 7.
Secondary Endpoints:

For the secondary endpoints the presence of several specified complications and interventions, one-year survival and laboratory values will be assessed in all patients until 12 months postoperatively:

**Non surgical category**

(1.) *Duration of hospital stay:*

Length of hospital stay [number of postoperative days] will be assessed at visit 5 (day of discharge). Causes of prolonged and/or complicated courses will be specified as followed:

*Surgical parameters:*

- Pancreatic fistula (ongoing yes/no)
- Delayed gastric emptying (ongoing yes/no)
- Bleeding (ongoing yes/no)
- Wound infection (ongoing yes/no)
• Abscess (ongoing yes/no)
• Cholangitis (ongoing yes/no)
• Other (please specify; ongoing yes/no)

General parameters
• Pulmonary (ongoing yes/no)
• Cardiocirculatory (ongoing yes/no)
• Renal (incl. urinary tract infection) (ongoing yes/no)
• Other (please specify; ongoing yes/no)

(2.) New onset of Diabetes:
Any new onset of Diabetes post surgery requiring any continuous insulin regimen over the study period.

(3.) One-year survival:
Is the patient still alive (yes/no) 12 months after primary surgical procedure?

Surgical category
(1.) Burst abdomen:
Postoperative missing continuity of the abdominal fascia with or without a wound dehiscence with consecutive relapse operation (complete or subcutaneous burst abdomen).

(2.) Wound infection:
Redness, wound dehiscence with secretion either of putrid or caliginous, smelly fluid or requiring antibiotic treatment.

(3.) Intra-abdominal fluid collection:
Intra-abdominal fluid collection of at least 5 cm or larger diameter observed at ultrasound or CT scan. This must be accompanied by a sterile culture and absence of pancreatic enzymes (amylases and lipases), outside the diagnosis of a pancreatic fistula.

(3.1) Sterile fluid collection of pancreatic origin:
Any intra-abdominal collection of at least 5 cm or larger diameter, confirmed by a morphological examination (US, CT scan) and/or a surgical re-intervention. The content of the fluid collection shows the presence of pancreatic enzymes and negative results of the bacteriological analysis (sterile culture).

(3.2) Infected fluid collection of pancreatic origin:
Any intra-abdominal collection of at least 5 cm or larger diameter, confirmed by a morphological examination (US, CT scan) and/or a surgical re-intervention. The content
of the fluid collection shows the presence of pancreatic enzymes and positive results of the bacteriological analysis (non-sterile/contaminated culture).

(4.) **Intra-abdominal abscess:**

Intra-abdominal collection of purulent or infected fluid (confirmed by culture) revealed by puncture under echographic or scanographic guide or confirmed by a surgical re-intervention, outside the diagnosis of a pancreatic fistula.

(5.) **Operating time:**

The total duration of the operation will be documented. Furthermore, the time period [min] between resection of the pancreatic tail and beginning of abdominal wall closure will be recorded in both treatment groups.

(6.) **Other Interventions (invasiver):**

Any procedure related to the primary operation with need for an incision of the abdomen or thorax either for a surgical procedure or placement of a drainage, e.g. due to intra-abdominal fluid collection.

3.12 Proposed sample size

A total of approximately 550 patients may be included with an expected pre-operative drop out rate of 100 patients. Thus, 450 patients will be randomized to accumulate 151 patients in both groups respectively for analyses (assumed protocol violations / lost to follow-up per group: 74 patients) The sample size will be recalculated after an interim analysis when 112 patients per arm are evaluable (see 4.1.2).

3.13 Assessment of safety

3.13.1 Specification of Safety Parameters

Definitions:

The term "adverse event" covers any sign, symptom, syndrome, illnesses that may impair the well-being of the subject during the period of observation in the clinical trial. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant. “Clinical relevance” will be defined as the existence of any endpoint or laboratory parameter out of range leading to a medical intervention. Medical interventions include all necessary medical, interventional and surgical procedures with direct causal relationship to the underlying complication. If the criteria of “clinical relevance are fulfilled, the AE documentation has to be done subsequently.
No causal relationship with the study intervention is implied by the use of the term "adverse event". Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Adverse events are categorized as non-serious and serious.

A serious adverse event is any adverse event which occurs at any time during the period of observation, that

- results in death
- is immediately life-threatening
- requires or prolongs hospitalization
- results in persistent or significant disability or incapacity
- requires medical or other intervention to prevent permanent impairment or damage.

3.13.2 Methods and timing for assessing, recording and reporting adverse events

At each visit between operation-day and day of discharge, day 30 and 12 months postoperatively (visit 4-6, see Flowchart section 1.10), the investigator will ask the patient if he or she suffered from any adverse events since the last visit. General practitioners (GP’s) have to be contacted before discharge of the study patient by the local study team (each participating centre). In order to realize good communication channels, basic data and requirements should be explained to the GP’s. It has to be stressed that every potential adverse event has to be reported to the local study team within 24 hours. Every patient will be provided with a small information-card (DISPACT-Card), which briefly comments basic principles, telephone numbers of the responsible local investigator/surgeon and the adverse event comittee/trial manager. Moreover, local investigators/surgeons have to declarate the participation in the DISPACT-Trial in every discharge letter.

Each adverse event has to be reported seperately in the adverse event form in the CRF.

Analysis of safety related data is performed with respect to

- Frequency of serious adverse events
- Frequency of all adverse events stratified by treatment
- Frequency of adverse events stratified by body-system or MedDRA SOC
- Frequency of adverse events stratified by severity
- Frequency of adverse events stratified by causality

The adverse event form contains:

Identification of the attending physician, description of the adverse event (event, beginning and duration, severity, outcome, causality to the intervention of the trial, therapy/interventions
taken), serious adverse event: yes/no, consequence for the trial, date and signature of the attending physician.

Classification of severity:
Mild: The adverse event does not interfere with routine activities. The patient may experience slight discomfort.
Moderate: The adverse event interferes with routine activities. The patient may experience significant discomfort.
Severe: The adverse event makes it impossible to perform routine activities. The patient may experience intolerable discomfort or pain.

Classification of causality:
Unrelated, possible related, probably related, definitely related: judged by the investigator

3.13.3 Emergency Procedures
In emergency situations, the investigator performs adequate therapy if necessary and controls the outcome of the patient.

3.13.4 Procedure for eliciting reports of and for recording and reporting adverse events
All adverse events occurring during the period between the day the subject has signed the informed consent document and Day 30 postoperatively (visit 6 by phone) must be documented on an “Adverse Event Form” in the CRF. All serious adverse events must be documented on a "Serious Adverse Event Form” in the CRF.
The principal investigator (Prof. M.W. Büchler) is responsible for the adequate documentation and reporting of serious adverse events. Serious adverse events have to be reported by the attending physician to the Independent Clinical Data Safety and Serious Adverse Manager (SDGC) within 24 hours after the incident. The principal investigator is responsible for reporting the serious adverse events to the independent ethics committee.

3.14 Expected Trial Duration
The duration of the whole trial is planned to be 54 months from start of recruitment to the reporting of results. It will be structured as follows:

- Duration of enrolment: 36 months
- Interim analysis: about 29th month
- Duration of treatment: Day of Surgery
- Duration of follow-up: 1 month for adverse events
12 months for survival

- End of follow-up period: 12 months after recruitment of the last patient
- Duration of analysis and reporting: The database will be closed 6 months after the end of follow up. Evaluations and reporting will be finished 6 months thereafter.
4 Statistics

4.1 Statistical methods
Statistical methods are used to assess the quality of data, homogeneity of treatment groups, endpoints and safety parameters of the compared surgical procedures, i.e. closure of pancreatic remnant after scalpel-resection by hand-sewn suture compared to stapler-closure after resection with the stapler. The estimation of the odds ratios of both techniques for developing a fistula is based on a Meta-analysis of studies with low number of patients and only one RCT. We must therefore assume that the estimators may be biased. Hence, in order to monitor the course of the trial, an adaptive design with interim analysis according to Bauer \(^{18-20}\) is planned to receive valid estimators of the odds ratios and therewith to reassess the sample size. The interim analysis on the primary endpoint and with respect to the safety parameters will be carried out by an independent biometrician, sworn to secrecy, and reported to the DSMB according FDA guidance on data monitoring committees \(^{21}\). Hence, the DSMB will advise the steering committee, in which way the study has to be continued. A detailed description will be given in the statistical analysis plan before closure of the data base for interim analysis.

4.2 Number of patients
The combined primary endpoint is the occurrence of a pancreatic fistula and/or all cause mortality until day 7 after the surgical operation. For details of assessment see section 3.10.1.1). On the basis of our meta-analysis, the point estimator for the fistula rate by scalpel transsection with hand-sewn suture is 35% (95% CI: 29% to 40%) and for stapler-transsection with stapler-closure 23% (95% CI: 15% to 31%). However, the estimators of the fistula rates specified by the Meta-analysis are based on uncertain data and assumed to be imprecise. The overall mortality after stapler-closure as well as after hand-sewn suture is expected to be rather low and seems not to be effected by the surgical method. Therefore, the calculated sample size is based on the estimators for the fistula rates from the Meta-analysis only. The hypothesis of no differences in the primary endpoint between the two surgical techniques will be tested by the Mantel-Haenszel-procedure (see 4.4). The sample size calculation is based on a two-sided continuity corrected \(\chi^2\)-test as the power of the Mantel-Haenszel-test, which is a summary \(\chi^2\)-test for stratified data, will be of the same size or higher.

The Meta-analysis provides an ARR estimate of about 12 % using stapler instead of hand-sewn suture. Because of the imprecise estimators we based our sample size calculation on an ARR of 15% and assumed the hand-sewn suture fistula rate of 35%. Herewith, we obtained a RRR of 43% which corresponds to an OR of about 0.464. Succeeding, to eliminate the disadvantages of
using the ARR with imprecise rate estimators, we will test the null hypothesis of these relative parameters.

Presuming a rate (fistula and/or death) of 35% after hand-sewn suture, at least 151 patients per group are required to detect a RRR of 43% (based on the estimated fistula rates) at a predetermined level of significance of 5% with a power of 80% (nQuery Advisor® release 4.0). A sample size of 151 patients per group guarantees a power ranging from 73% to 83% depending on the level of the fistula rate in the range of 29% to 40% after hand-sewn suture and considering an OR of 0.464.

4.3 Potential for recruitment of suitable patients

Assuming a preoperative drop out rate of 15% (before randomisation), and a postoperative drop out rate of 10%, respectively, approximately 500 eligible patients have to be screened. Thus, 336 patients have to be randomised to accumulate a number of 302 patients for the analysis (assuming 17 patients lost to follow up/per group). Recruitment of patients will be realized by up to 20 participating high-volume centers with at least 10 distal pancreatic resections per year. Regarding different frequencies distal pancreatectomies in each center, a recruitment of approximately 8 patients per center and year is considered to be practicable. Assuming a total number of 15 participating centres, an overall recruitment period of 36 months is considered to be necessary to enrol the sufficient number of patients (Figure 3).

Figure 3: Flowchart DISPACT-Trial according to CONSORT
Recruitment plan:
The overall recruitment is scheduled to be as followed:
Considering a consecutive initialization of participating centers in the first year 15% of the overall patients should be recruited in the first 12 months. In the second and third year, recruitment of the lacking 85% of patients is considered to be practicable.

Figure 4: Recruitment plan (overall patients/36 months)

4.4 Analysis

Analysis of the primary endpoint
The primary endpoint of the trial is the combined endpoint, occurrence of a pancreatic fistula and/or all cause mortality until postoperative day 7 (Definition, see section 3.10.1.1). The hypothesis of no differences in this endpoint between the two surgical techniques will be tested confirmatory by the Cochrane-Mantel-Haenszel-procedure allowing for the possibly confounding factor surgical expertise (respectively factor surgeon) (see section 3.8.4). Stratification by centre and risk level (low/high) will be done by randomisation to guarantee homogeneous distribution of both techniques in these groups (see section 3.8.2). Taking into account center effects in addition to the factor surgeon is not necessary because the fittings and conditions regarding these operation procedures are similar in each center. Furthermore, no effects are expected through the four underlying indications, because closing pancreatic remnant after resection of diseased tissue is executed in intact tissue, so that the conditions for developing a fistula are the same for all indications. Nevertheless, to exclude defalcation of indication effects, an explorative analysis will be done. With the results of the meta-analysis, a superiority of hand-sewn suture over stapler-closure can not be excluded; therefore a two-sided adaptive test.
plan is used. Let ψ denote the common odds ratio taking into account the stratification according to the categories of surgical expertise, then the null hypothesis to be tested is as follows:

\[ H_0: \psi = 1 \quad \text{versus} \quad H_1: \psi \neq 1. \]

The interim analysis with sample size adaption

Because of the uncertainty of the OR estimates under-powering is possible. Thus, an adaptive design with interim analysis (getting better estimators) was chosen to improve power by reassessing the sample size. The adaptive design with interim analysis will be performed according to the two-stage approach described by Bauer \(^{18-20}\). To receive good estimates, the interim analysis will be performed place when 2/3 (112 patients per arm) of the patients are evaluable. As described in detail by Wassmer \(^{22}\) in a two-stage Bauer-Köhne-design addressing a two-sided problem, it is a valid procedure to perform two one-sided tests to the level \(\alpha/2\) (see Wassmer \(^{22}\) section 3.1.5, p 111f and Fig. 3.7). Therefore, the choice of significance level is \(\alpha = 0.05\). Critical values for Fisher’s combination test were selected using ADDPLAN 2.0 \(^{23}\). With the results of the Meta-analysis, an ARR of 7% is defined as clinical relevant so that stopping for futility does not make sense. Hence, in consideration of this the critical values for stage one are \(\alpha_1=0.01019\) or \(1-\alpha_1=0.98981\) \((\alpha_0=0.5, \text{two-sided test})\). Let the resulting p-value on stage one be denoted by \(p_1\). Then the approach procedes as follows:

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<thead>
<tr>
<th>Result on first stage</th>
<th>Consequence</th>
</tr>
</thead>
</table>
| \(p_1 \leq 0.01019\) or \(p_1 \geq 0.98981\) | Stopping of the trial; Rejection of \(H_0\)  
In case \(\psi_1 < 1\): Superiority of stapler-closure with respect to a reduction of the rate of fistulae (and/or all cause mortality) has been proven.  
In case \(\psi_1 > 1\): Superiority of hand-sewn suture with respect to a reduction of the rate of fistulae (and/or all cause mortality) has been proven. |
| 0.01019 < \(p_1\) < 0.98981 | Continuation of the trial; New estimation of the fistula rates, recalculation of the sample size and sample size adaptation if necessary and feasible (see below). |
In case $0.01019 < p_1 < 0.98981$, the trial will be continued and the sample size will be recalculated as follows: The required number of patients will be recalculated replacing the assumptions initially made by the estimators obtained in the interim analysis. According to Bauer, the calculation of the further sample size may be based on the critical level $c_{\alpha/2}/p_1$. The number of patients to be included at stage two will be adjusted by the proportion of the ITT-population referring to all enrolled patients. The recalculated sample size will be provided to the independent DSMB with the interim report. This board will give advice whether and how an additional recruitment of patients will be feasible. If the trial will be continued, the required subsample of patients will be recruited.

*Structure of the final statistical analysis*

After the additional patients have completed the trial, that is, the end of stage two, the test statistic and the p-value $p_2$ will be calculated for the set of patients in stage two. $H_0$ will be tested again using Fishers rule with the product of the p-values of both stages. The critical value for the combination test is given as $c_{\alpha/2} = 0.0038$. Let $p_2$ denote the resulting p value and $\psi_2$ denote the estimator for the common odds ratio based on these patients. The final decision, whether $H_0$ to reject or not, will be taken as described:

<table>
<thead>
<tr>
<th>Combined results</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1*p_2 \leq 0.0038$ or $(1-p_1)(1-p_2) \leq 0.0038$</td>
<td>Rejection of $H_0$ In case $\psi_2 &lt; 1$: stapler-closure is superior with respect to a reduction of the rate of fistulae (and/or all cause death) In case $\psi_2 &gt; 1$: hand-sewn suture is superior with respect to a reduction of the rate of fistulae (and/or all cause death)</td>
</tr>
<tr>
<td>otherwise</td>
<td>No rejection of $H_0$</td>
</tr>
</tbody>
</table>

*Estimation of treatment effect*

The common treatment effect will be estimated by the common odds ratio for both stages and corrected for bias through interim analysis $^24$. The appropriate 95%-confidence intervals will be
given. A logistic regression will be done including the factors surgical technique and surgical expertise to explore the possible influence of these factors.

**Analysis of the secondary endpoints, baseline characteristics and other variables**

All demographic and safety parameters which are included in the interim analysis will be analyzed separately for both stages of the trial as well as for all patients. All other variables will only be analyzed for the whole trial population.

The analyses of secondary endpoints and baseline characteristics are descriptive. Listings and tables will be prepared according to the ICH-E3-guideline. All measurements taken will be listed. Continuous variables will be described at least by the number of observations, mean, standard deviation, median, minimum and maximum for the trial population and separately for both treatment groups. The description of categorical variables will include, at least, the number and percentage of patients belonging to the relevant categories for the trial population as well as for both treatment groups. Appropriate tests ($\chi^2$-test, Wilcoxon rank-sum test, or t-test, respectively) will be performed to compare both treatment groups, and p-values (explorative) will be given. In addition, graphical methods will be applied to present the observed data. The rating of relevance of outcome parameters by patients will be recorded at the day of the screening and inclusion. Surgeons will be asked for their rating at the time of inclusion of their first trial patient. The rank order of endpoints will be presented for each patient and each surgeon. Moreover, the sum of ranks for each endpoint will be given separately for patients and surgeons.

**Additional analyses**

An accompanying logistic regression will be done in order to study the effect of further covariates such as center, surgical expertise, indication and grade of fibrosis on the primary endpoint. Moreover a mixed effects model model on the primary endpoint using the individual surgeon as a random incept will be fitted with the data. This analysis will be done to generalize the results to the population of surgeons.

4.5 Analysis populations

Interim and final analyses are performed on the basis of an intention to treat (ITT) population with respect to ITT principles. All randomized patients will be included in the ITT-analysis (ITT population). Additionally, in the final analysis, a per-protocol analysis for the primary endpoint will be made including only patients without a protocol violation (PP population).
<table>
<thead>
<tr>
<th>Analysis population</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>All randomised patients</td>
</tr>
</tbody>
</table>
| PP population       | As for ITT and absence of major protocol violations:  
|                     | a) Violation of inclusion or exclusion criteria  
|                     | b) Resection of the pancreatic tail by application of surgical techniques other than stapler or suture-closure  
|                     | c) Attending surgeon did not comply with the defined surgical procedure |

Patients ending the trial before randomisation will be described as separate group, if appropriate data are available. In case of an early stopping of the trial, a final analysis will be done in which all patients will be added who were recruited during the time of the implementation of the interim analysis.
5 Ethical Considerations

5.1 Approval of the Clinical Trial Protocol and Amendments
Before the start of the trial, the clinical trial protocol, the informed consent document, and any other appropriate documents will be submitted to the independent ethics committee. Before the first subject is enrolled in the trial, all ethical and legal requirements will be met. The independent ethics committee will be informed of all subsequent protocol amendments. Amendments will be evaluated to determine whether formal approval must be sought before implementation and whether the informed consent document should also be revised. There will be no deviation from the protocol without an amendment. An amendment has to be a written document, prepared in agreement with the principal investigator and the sponsor. After submission and approval by the Ethics Committee the amendment has to be signed by the Steering committee.
The SDGC will keep a record of all communications with the independent ethics committee.

5.2 Risk-/benefit ratio for participants
Until now, data concerning the current techniques have not shown a statistically significant superiority of one technique. Stapler-transsection with stapler-closure and scalpel transsection with hand-sewn closure of the pancreatic remnant, are both known to be standard procedures in distal pancreatectomy. Our meta-analysis of these techniques showed a non-significant trend in favor of the stapler technique. Therefore, the two most commonly used techniques will be compared in this trial. The prognosis of the two treatment groups in malignant and benign diseases of the pancreas is not influenced because of similar resection techniques (equal treatment) in both groups. Furthermore, no additional investigations and interventions are planned. Therefore, the risks for the participants involved in this trial are similar to every patient undergoing distal pancreatectomy outside the trial (e.g. bleeding, wound infection and pancreatic fistula). The potential benefit for the participants is a surgical standardized treatment and follow-up of high quality, as participating centers are all highly specialized.

5.3 Declarations
This study is accomplished according to the Helsinki Declaration in its actual version, the Medical Association’s professional code of conduct, the principles of the Good Clinical Practice (GCP) and the Federal Data Protection Act. The trial will also be carried out under local legal and regulatory requirements.
5.4 Subject Information and Informed Consent

Before a patient can be admitted to the clinical trial, the subject must give written and oral informed consent to participate after nature, scope, and possible consequences of the clinical trial have been explained precisely and clearly to her or him. An informed consent document including both information on the trial and the informed consent form will be prepared and given to the subject. This document will consider all local requirements. The document is written in a language understandable to the subject and has to indicate name of the person who informed the subject. This person must be a physician.

After reading the informed consent document and sufficient time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial, the subject has to give written consent. To ensure validity, the subject's consent has to be confirmed at the time of consent by the personally dated signature of the subject. A copy of the signed consent document will be given to the subject or the subject's legally authorized representative. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical trial until a valid consent has been obtained.

5.5 Opinion from the Ethics Committee

Not yet available.

6 Trial Management and Organization

6.1 Study coordination and data management

The study coordination, the data management, and analysis are performed by the SDGC and the IMBI. The responsibilities comprise:

- Provision of the data forms (Case Report Forms (CRF))
- Database design and its updating, data entry, data correction
- The randomization process
- Monitoring and timely data acquisition
- Handling of adverse events reports
- Intending an independent biometrician for the interim analysis and its communication to the Steering Committee
- Final analysis and its communication to the Steering Committee
- Regular information to all participating centers on the status of enrollment and particular observations.
6.2 Expertise of those responsible for the trial
This multi-center trial is a project of the Study Center of the German Surgical Society (Studienzentrum der Deutschen Gesellschaft für Chirurgie – SDGC) the University of Heidelberg and by the Institute of Medical Biometry and Informatics of the University of Heidelberg (IMBI). From 2001 the Department of Surgery, University of Heidelberg conducted and participated in more than 28 clinical trials (pharmacutical and investigator driven surgical trials). The IMBI has some twenty years of experience concerning methodological and biometrical support of clinical trials and has been involved in more than 60 mainly multi-center clinical trials and numerous scientific publications. Prof. Büchler has authored and co-authored more than 50 international scientific papers on the technique and results of pancreatic surgery. Dres. Seiler and Knaebel have gathered experience in evidence-based surgery and referenced several articles and lectures. The group of clinical sites chosen for this trials consists of the most renown pancreatic surgeons throughout Germany and Europe.

6.3 Supporting infrastructure of the medical institution(s)
This protocol is the basis for the application for the Study Center of the German Surgical Society (SDGC). This grant will enable the necessary infra-structure to successfully implement and execute clinical multi-center trials in surgery. The proposed trial shall be one of the first two multi-center model projects that will be supported by the newly founded SDGC. The SDGC will include the existing cooperation unit “Biometry and Data Management” of the IMBI. Quality assurance will be done in cooperation by the SDGC and the IMBI.

6.4 Independent Biometrician
Dipl.-Inform. Med. Andreas Deckert (IMBI) is the independent Biometrician. He is responsible for the interim analysis on the primary endpoint and with respect to the safety parameters.

6.5 Committees
6.5.1 Steering Committee

Tasks of the Steering Committee
- Review of the study protocol before the beginning of the study and review of protocol changes.
- Evaluation of the DSMB recommendations regarding premature study discontinuation.
In summary, the Steering Committee is responsible for the implementation of the study. All other committees report to the Steering Committee.

*Participants Steering Committee Dispact Trial*

Prof. Dr. Dr. h.c. Christian Herfarth, MD  
Prof. Dr. Dr. h.c. Markus W. Büchler, MD  
Prof. Dr. Hans Jürgen Schlitt, MD  
Dr. Christoph M. Seiler, MD MSc  
Dr. Hanns-Peter Knaebel, MD  
Prof. Dr. Helmut Friess, MD  
Dr. Markus K. Diener, MD  
Dr. sc. hum. S. Witte

6.5.2 Data and Safety Monitoring Board (DSMB)

*Tasks of the DSMB are:*

- Monitoring the course of the study, the safety aspects and the primary study parameters.
- Reviewing the results of the interim analysis
- Recommending the Steering Committee whether the study should be continued modified or discontinued.

The members are not allowed to have any relation in any other way with the study.

*Participants DSMB Dispact Trial*

Prof. Dr. Christian Ohmann  
Dr. Stefan Sauerland, MD MPH  
Prof. Dr. Istvan Klempa, MD

6.5.3 Data Verification Committee

The Data Verification Committee will verify the correctness of the inclusion criteria, and the surgical and data monitoring.

*Participants Data Verification Committee Dispact Trial*

Dr. Markus K. Diener, MD  
Dr. Christoph M. Seiler, MD MSc  
PD Dr. Peter Kienle, MD
6.5.4 Adverse Event Committee

The task of the Adverse Event Committee is the regular review and classification of all reported adverse events, and to inform the Steering Committee and the DSMB as needed.

Participants Adverse Event Committee Dispact Trial

Dr. Hanns-Peter Knaebel, MD
Dr. Moritz N. Wente, MD
Dr. Jörg Köninger, MD
7 Monitoring and Quality Assurance

7.1 Quality control and quality assurance
The design of the underlying protocol represents a randomized-controlled multi-center trial with a sufficient number of patients to be analyzed. Rigorous planning and implementation promise results at the highest level of evidence. Trial design, standardization of treatment groups, surgical and data monitoring will ensure a high quality of the collected data. Quality control and assurance is also backed up by the application of the standard operating procedures of the SDGC (trial management), the KKS (monitoring) and the IMBI (biostatistics).

7.2 Monitoring
An independent monitoring team of the SDGC (Data Verification Committee – see 6.5.3) will check at random whether the specified procedures are followed. Moreover, a continuing on-site data monitoring is planned and will be conducted at least three times during the enrolment period in each participating centre. The expertise of the participating surgeons will be documented before and during the trial as well as the level of medical care of the participating institutions. Surgical monitoring will be achieved by photo-documentation (intraoperative digital photo-documentation) of the crucial steps of the procedure (see section 3.8.4 photo documentation).

7.3 Data handling and record keeping
All protocol-required information collected during the trial must be entered by the investigator, or a designated representative, in the eCRF. The investigator, or a designated representative, should complete the eCRF pages as soon as possible after the information is collected, preferably on the same day when a trial subject is seen for an examination, treatment, or any other trial procedure. Any pending entries must be completed immediately after the final examination. Explanation should be given for all missing data.

The cooperation unit IMBI/SDGC will check completeness, validity and plausibility of data by validating programs, which will generate queries. The investigator or the designated representatives are obliged to clarify or explain the Queries. The data management is accomplished with the appropriate SOPs valid in the IMBI.

7.3.1 Direct access to source data / documents
Patient data will be documented pseudonymously. Access to source data is only permitted in case of trial-related monitoring, audits, reviews by the independent ethics committee, and regulatory inspections. The patient’s written agreement in the informed consent is mandatory.
7.3.2 Handling of missing, unused and spurious data
Assessment of the primary endpoint is expected to be complete, due to the short time period from operation to assessment (7 days). Moreover, all patients usually have to stay in hospital for at least 8-10 days after the operation. Nevertheless, patients discharged before day 7 are considered as treatment failures, if no information for day 7 is available. A sensitivity analysis will be added to estimate worst case and best case scenarios for drop outs.

7.4 Procedures for reporting deviations from the statistical plan
The investigator must inform the coordinating data center and the responsible Ethics Committee of any protocol deviation in order to protect the life or physical well-being of a patient in case of emergency. Such a notification should be made as rapidly as possible, no later than 5 working days after the emergency. Except for such emergencies, the prior consent of the Steering Committee and of the respective Ethics Committee must be obtained in case of changes of or deviations from the study protocol.

7.5 Maintenance of trial treatment randomization codes and procedures for unblinding
The treatment allocation of the study patients will not influence additional treatment in case of occurrence of adverse events. Therefore, the randomization sequence, allocation concealment and blinding will be maintained for all study patients.

7.6 Criteria for termination of the trial
The principal investigator has the right to terminate the trial and to remove all trial material from the trial center at any time in consultation with the Steering Committee and the Biometricians. If a termination of the trial becomes necessary, the steering committee of the trial will discuss this issue with the independent DSMB. Reasons that may necessitate a termination of the trial include the following:

- The incidence or severity of adverse events in this trial indicates a potential health hazard caused by the study treatment.
- It appears that patients’ enrolment is unsatisfactory with respect to quality and/or quantity or data recording is severely inaccurate and/or incomplete.
- External evidence demanding a termination of the trial.
- Recommendation of the DSMB due to results of the interim analysis.
8 References


9 Supplements

9.1 Signature sheet

This study protocol was subject to critical review. The information it contains is consistent with the current risk-benefit evaluation of used surgical procedures and the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of ICH-GCP.

Date: ______________ Signature: ___________________ _________________________
Name:  Prof. Dr. Christian Herfarth
Function: Steering committee

Date: ______________ Signature: ___________________ _________________________
Name:  Prof. M. W. Büchler
Function: Principal Investigator/Steering Committee

Date: ______________ Signature: ___________________ _________________________
Name:  Prof. Hans Jürgen Schlitt
Function: Steering committee

Date: ______________ Signature: ___________________ _________________________
Name:  Dr. med. Hans-Peter Knaebel
Function: Steering Committee

Date: ______________ Signature: ___________________ _________________________
Name:  Dr. med. Christoph M. Seiler, MSc
Function: Steering Commitee

Date: ______________ Signature: ___________________ _________________________
Name:  Prof. Helmut Friess
Function: Steering committee

Date: ______________ Signature: ___________________ _________________________
Name:  Dr. med. Markus K. Diener
Function: Trial Coordinator/Steering Commitee

Date: ______________ Signature: ___________________ _________________________
Name:  Dr. sc. hum. Steffen Witte
Function: Steering Committee
9.2 Publication policy
The steering committee and the trial management commits to writing a scientific publication in any case even in case of early stopping of the trial after the first stage. The design and the final results of the trial will be published and the authorship will be assigned by the trial management. At least one co-worker of the co-operating institute IMBI will be part of the principal authors. Each participating center who contributes to this trial will be mentioned.

9.3 Authors contributions:
Diener MK, Seiler CM and Knaebel HP designed and wrote the trial protocol, Witte S and Deckert A prepared bio-statistics of the trial and are in charge of the data management, Büchler MW acts as principal investigator and provides the necessary infrastructure for the protocol development.

9.4 Conflicts of interest
All applicants disclose any financial and/or personal relationships with other persons and organisations which might impair the independence of their work.

9.5 Agreements
The underlying protocol is intellectual property of the Clinical Study Center of the German Surgical Society (SDGC). Publication of results is kept by the authors of this protocol and co-workers of IMBI, University of Heidelberg, Germany. All participating trial sites will be mentioned in case of publication.

9.6 Co-financing by industry and / or other third parties
All study material used during the surgical procedure (e.g. stapling devices and suture material) will be provided by ETHICON™ Endo Surgery, Norderstedt, Germany.

9.7 Patient Insurance
Company details not yet available
9.8 Informed Consent

Patienteninformation / Merkblatt

Pankreaslinksresektion – eine randomisierte kontrollierte Studie zum Vergleich von zwei chirurgischen Techniken
Distal Pancreatectomy – A randomised controlled Trial to compare two different surgical techniques

DISPACT - Trial

Sehr geehrte, liebe Patientin,
Sehr geehrter, lieber Patient,

Sie wurden in unsere Klinik auf Grund einer Erkrankung der Bauchspeicheldrüse aufgenommen, die durch eine Operation demnächst behandelt werden soll.

Wir wollen sie einladen, an einer Studie teilzunehmen, welche zwei der am häufigsten angewendeten Operationstechniken zur Entfernung des Pankreaswanzes miteinander vergleicht.


Was ist der Zweck der Studie?

Ziel dieser Studie ist es, zu untersuchen, welche Operationstechnik am geeignetsten ist, die postoperative Rate an Pankreasfisteln so gering wie möglich zu halten.

Abbildung 1: Entfernung des Pankreasschwanzes und Versorgung der Rest-Bauchspeicheldrüse

_Nutzen und Risiken der Behandlung_

_Was geschieht mit mir, wenn ich an der Studie teilnehme?_
**Studienvisiten:**

**Begleituntersuchungen:**

**Nachbeobachtung:**
30 Tage bzw. 12 Monate nach der Operation werden wir Sie bzw. ihren Hausarzt telefonisch zum Stand Ihrer Genesung befragen und klären, ob sich Komplikationen oder unerwünschte Nebenwirkungen der Therapie entwickelt haben.

**Freiwilligkeit, vorzeitige Beendigung der Teilnahme und Datenschutz:**

**Haben Sie weitere Fragen?**
Sollten Sie noch weitere Fragen zu Ihrer Erkrankung, den eingesetzten Behandlungsmethoden oder dem Studienablauf haben, so zögern Sie nicht, diese Ihrem behandelnden Arzt zu stellen. Man wird diese Fragen gerne ausführlich beantworten.
Wir bedanken uns für Ihre Unterstützung

Dieses Dokument ist für den Verbleib bei Ihnen bestimmt
**Einverständniserklärung**

Ich bin über Sinn, Bedeutung und Verlauf der Studie sowie über mögliche Belastungen und Risiken anhand der schriftlichen Patienten--Information, die ich erhalten habe, und in einem Gespräch mit Herrn / Frau ________________ aufgeklärt worden. In diesem Zusammenhang sind mir alle meine Fragen vollständig beantwortet worden.


**Ich wurde darüber aufgeklärt und stimme zu, dass die im Rahmen dieser Studie erhobenen Daten in pseudonymisierter Form dokumentiert werden und dass Dritte nur zur Überprüfung und Auswertung der Studiendaten Einblick in die Originalunterlagen erhalten.**

Bei Rücktritt von der Studie bin ich mit der Auswertung des schon gewonnenen Materials und der schon vorhandenen Daten einverstanden (Zutreffendes bitte ankreuzen):

- [ ] Ja
- [ ] Nein.

Ich bin mit der anonymisierten feingeweblichen Begutachtung des entfernten Bauchspeicheldrüsenanteils im Rahmen der DISPACT-Studie einverstanden. Ich stimme in diesem Zusammenhang der Versendung einer Gewebeprobe eines Teils des entfernten Bauchspeicheldrüsenschwanzes an das Europäische Pankreaszentrum (EPZ), Universitätsklinikum Heidelberg, zu.

- [ ] Ja
- [ ] Nein.

_____________________________  __________________________
Vor-/Nachname des Patienten  Geburtsdatum
(in Druckbuchstaben)

_____________________________
Unterschrift des Patienten  Aufklärungsdatum (vom Patienten einzutragen)

_____________________________
Vor-/Nachname des Studienarztes (in Druckbuchstaben)  Aufklärungsdatum (vom Studienarzt einzutragen)

_____________________________
Unterschrift des Studienarztes
9.9 Standard surgical procedures of distal pancreatectomy – Operation manual

Vorbereitende Schritte:

- Rückenlagerung des Patienten
- Dreifache Wischdesinfektion des Op-Feldes
- Steriles Abdecken
- Antibiotikaprophylaxe mit z.B. single-shot Mezlocillin i.v.(z.B. Baypen) 4g + Metronidazol i.v. (z.B. Clont) 500mg oder double-shot bei OP-Dauer > 4 Stunden (according to local standards).
- Eventuelle Octreotid-Applikation (z. B. Sandostatin 100µg s.c.). Je nach lokalem Standard.
- Randomisation des Studienpatienten, wenn Einschlusskriterien weiterhin erfüllt.

Operation:

- Exploration: Prüfen der Indikation zum kurativ-chirurgischen Vorgehen (Peritonealkarzinose?, Lebermetastasierung?). Im Falle einer palliativen Situation ist dies zu dokumentieren, Patient verbleibt jedoch nach Randomisation in der Studie (ITT-Prinzip).
- Eröfnen der Bursa omentalis durch Separation des Lig. gastrocolicum und Darstellung des Pankreaskörpers- sowie auch Schwanzes. Darstellung und Exploration der Raumforderung des Pankreasschwanzes links-lateral der Vena mesenterica superior.
- Komplette Freilegung des Pankreas, Kochermanöver, so dass der Pankreaskopf unterfahren werden kann. Exploration des Pankreaskopfes.
- Darstellung der V. mes. sup. am Pankreasunterrand und Anlage von zwei Haltefäden. Untertunnelung des Pankreas auf der V. mes. sup.
- Präparation des Pankreaseoberrandes und Anlage von zwei Haltefäden am Durchtritt der V mes. sup. und Untertunnelung mit einem Zügel. Komplettierung der Mobilisierung am
Pankreasoberrand unter Darstellung des Truncus coeliacus und des Abgangs der A. lienalis. Absetzen der A. lienalis und Durchstechungs ligatur im Falle der Splenektomie.

- **Staplerresektion:** Absetzen des Pankreasschwanzes mit dem Klam mernah tgerät (Ethicon TL 60 1.0 – 2.5 mm). Gewinnen einer Gewebeprobe zur histologischen Auswertung. Bei Randomisation zur Stapler-Resektion darf kein weiterer Nahtverschluß am verbleibenden Pankreasrest erfolgen. Als Ausnahme gilt nur die Applikation von singulären Ligaturen / Durchstechungen der Staplernaht zur Blutstillung.

- **Handnaht:** Absetzen des Pankreasschwanzes mit dem Skalpell. Der Stumpfverschluß erfolgt mittels gezielter Durchstechung des Pankreasganges, gefolgt von Übernähung des Pankreasstumpfes (Einzelknopf- oder fortlaufende Nahttechnik) mit langsam resorbierbarem, monofillem Faden (z.B. PDS oder Monoplus) der Stärke 4/0 oder 5/0 USP. Gewinnen einer Gewebeprobe zur histologischen Auswertung.

- Lavage des Abdomens und Kontrolle auf Blut trockenheit.
- Einlage von Drainage/n in das Resektionsgebiet und Ausleitung über den Unterbauch.
- Schichtweiser Bauchdeckenverschluss und steriler Wundverband.

**Postoperative Standards:**
- Fortführung der Octreotidmedikation (z. B. Sandostatin 3x100µg s.c. über 5 Tage) nach lokalem Standard
9.10 Screen Log DISPACT-TRIAL

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<tr>
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<th>Investigator</th>
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10  FINANCIAL PLAN

<table>
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<tr>
<td>Case-based lump sum (per patient) á 500,- €</td>
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</tr>
<tr>
<td>Trial supervisor (Senior Surgeon / Investigator)</td>
<td>Scientific and regulatory support: initiation visit, continuing management of incoming AEs/SAEs, final data analysis.</td>
<td>92.500 €</td>
</tr>
<tr>
<td>BAT Ib (first and last 12 months = 24 months)</td>
<td>46.250 € / year</td>
<td></td>
</tr>
<tr>
<td>Coordinating Physician / Investigator</td>
<td>Scientific support: initiation visit, observation of protocol conform treatment</td>
<td>190.000 €</td>
</tr>
<tr>
<td>BAT IIa (60 months)</td>
<td>38.000 € / year</td>
<td></td>
</tr>
<tr>
<td>Coordinating Study Nurse</td>
<td>Administrative support: continuing communication, newsletters, monitoring, data administration, preparation, coordination and post-processing of study meetings</td>
<td>162.000 €</td>
</tr>
<tr>
<td>BAT III ¾ (60 months)</td>
<td>32.400 € / year</td>
<td></td>
</tr>
<tr>
<td>Workstation x 3</td>
<td>Trial Supervisor, Coordinating Investigator, Coordinating Study Nurse</td>
<td>15.000 €</td>
</tr>
<tr>
<td>Investigator File</td>
<td>Implementation, maintenance; incl. all templates etc.</td>
<td>3.060 €</td>
</tr>
<tr>
<td>Study Protocol, investigator binder, patient checklists</td>
<td>Expenses for printing, binding and shipping of study protocols and investigator binders</td>
<td>10.000 €</td>
</tr>
<tr>
<td>3 per centre = 60 protocols</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generation and maintenance Trial Master File</td>
<td>Complete documentation of study related functions</td>
<td>2.450 €</td>
</tr>
<tr>
<td>Shipping/mailing histological samples (a 550 study patients)</td>
<td>Central histological assessment of specimens</td>
<td>8.250 €</td>
</tr>
<tr>
<td>1 shipping per centre / year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Histological Specimen Tubes (550 samples á 2 resection margins)</td>
<td>1100 €</td>
<td></td>
</tr>
<tr>
<td>Central histological assessment of specimens</td>
<td>3.300 €</td>
<td></td>
</tr>
<tr>
<td>Histological Analysis (Grade of fibrosis)</td>
<td>1100 €</td>
<td></td>
</tr>
<tr>
<td>HE staining of tissue samples</td>
<td>66.000 €</td>
<td></td>
</tr>
<tr>
<td>General expenses for Coordination and Communication Administration, Logistics and infrastructure (60 months)</td>
<td>35.000 €</td>
<td></td>
</tr>
<tr>
<td>Paper, envelopes, file folders, toners (fax and printer), cd-roms, telephone and fax charges (60 months), status reporting</td>
<td>10.000 €</td>
<td></td>
</tr>
<tr>
<td>Fees local advisory board (a 20 centres)</td>
<td>10.000 €</td>
<td></td>
</tr>
<tr>
<td>Patient Insurance</td>
<td>41.250 €</td>
<td></td>
</tr>
<tr>
<td>550 patients x 75€</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sub-total</strong></td>
<td>638.810 €</td>
<td></td>
</tr>
</tbody>
</table>

**Study Meetings**

- 4 National Study Meetings á 60 participants
  - 2 participants per centre = 40 centre participants
  - 20 study coordination participants
- Expenses for convention centres (5.000 x 4 Meetings) = 20.000 €
- Daily lump sums 60€ x (60 persons x 4 Meetings = 240) = 14.400 €
- Travelling expenses (60 persons x 4 Meetings = 240)
  - Inland*: 350€ x (14 centres á 2 participants x 4 Meetings = 112) = 39.200 €
  - Foreign Countries**: 1350€ x (6 centres á 2 participants x 4 Meetings = 48) = 64.800 €
- Study Coordination Team 350€ x (20 per meeting = 80) = 28.000 €
- Material 30€ x (60 persons x 4 Meetings = 240) = 7.200 €
- **Meeting brochure**

**Sub-total** = 173.600 €

**Study monitoring**

- Monitoring Manual
  - Implementation and maintenance = 1.600 €
- Continuing surgical/data monitoring
  - Maintenance of protocol conform treatment: Balancing of source data with CRF documentation, inspection of AE/SAE Management, Clinical Site Support, Final Report = 133.800 €
- 3 per center (20 centres): Initiation, Interim, Close Out Visit
- 2 days / visit (incl. preparation, post-processing and reporting)
- Travel expenses monitoring visits
  - 14 x 3 = 42 visits in Germany
  - Average hotel fee per day: 70 €
  - Travel expenses public transport: 20 €

**Sub-total** = 27.060 €
<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average railway fee (2nd class): 80 €</td>
<td></td>
</tr>
<tr>
<td>Daily lump sum: 25€</td>
<td></td>
</tr>
<tr>
<td>⇒ 220 € per visit x 42 = 9240</td>
<td></td>
</tr>
<tr>
<td>6 x 3 = 18 visits foreign countries</td>
<td></td>
</tr>
<tr>
<td>Average hotel fee per day: 70 €</td>
<td></td>
</tr>
<tr>
<td>Travel expenses public transport: 50 €</td>
<td></td>
</tr>
<tr>
<td>Average flight expenses: 800 €</td>
<td></td>
</tr>
<tr>
<td>Daily lump sum: 35 €</td>
<td></td>
</tr>
<tr>
<td>⇒ 990 € per visit x 18 = 17,820 €</td>
<td></td>
</tr>
<tr>
<td>Digital camera for surgical monitoring</td>
<td>Documentation of surgical procedure/each participating centre</td>
</tr>
<tr>
<td>á 300,- € per centre (20 centres)</td>
<td>6,000 €</td>
</tr>
<tr>
<td>Continuing Centre Support</td>
<td>Ongoing communication and support beyond regular monitoring visits, query management, status reports</td>
</tr>
<tr>
<td>5 DSMB Meetings (á 3 members)</td>
<td>Supervision of monitoring, review of interims analysis, discontinuation</td>
</tr>
<tr>
<td>Reimbursement / travelling expenses</td>
<td>22,500 €</td>
</tr>
<tr>
<td>1.500 € per person / meeting <em>/</em>*</td>
<td></td>
</tr>
<tr>
<td>Sub-total:</td>
<td>235,380 €</td>
</tr>
</tbody>
</table>

**Data Management and Biometrics**

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentary</td>
<td>eCRF, database, database quality control, validation plan, query programming, data entry support, foto documentation, programmino of status reports, interim analysis, final analysis</td>
</tr>
<tr>
<td>BAT III ½ (60 months)</td>
<td>118,800 €</td>
</tr>
<tr>
<td>Biometrics</td>
<td>Design, protocol development, database structure, analysis plan, interim report, status reports, meetings, data quality control, final analysis, biometrical report, publication</td>
</tr>
<tr>
<td>(3x8months BAT Ib = 24 months BAT Ib),</td>
<td>92,500 €</td>
</tr>
<tr>
<td>(1.Planning-Phase, .2.Interim-Phase, 3.Final-Phase)</td>
<td></td>
</tr>
<tr>
<td>(Senior Biometrician due to sophisticated methods)</td>
<td></td>
</tr>
<tr>
<td>Online Data Entry</td>
<td>Implementation of validated remote data entry tool</td>
</tr>
<tr>
<td>Randomization, (550-5)*5</td>
<td>16,500 e</td>
</tr>
<tr>
<td>Subtotal</td>
<td>230,275 €</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td>1,553,065 €</td>
</tr>
</tbody>
</table>
Supplements:

* Travel expenses within Germany including railway fees (2nd class), expenditure of time and accommodation costs.

** Travel expenses from outside Germany/ to foreign centres including flight and railway fees (2nd class), accommodation costs and daily catering lump sum.