RECOPS-Study

The Effect of Braun Enteroenterostomy on the Postoperative Outcome after Pylorus-preserving Pancreaticoduodenectomy

Short Title: RECOPS

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I. Signatures

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II. Synopsis

Title	The effect of Braun enteroenterostomy on the postoperative outcome after pylorus-preserving pancreaticoduodenectomy.
Short title	RECOPS
Aims	The clinical study aims to analyse the impact of an additional Braun enteroenterostomy in patients after pylorus-preserving pancreaticoduodenectomy followed by standard Child reconstruction compared to patients undergoing pylorus-preserving pancreaticoduodenectomy followed by standard Child reconstruction.
Intervention	**Experimental Intervention:** Patients after pylorus-preserving pancreaticoduodenectomy followed by Child reconstruction and an additional Braun anastomosis between afferent and efferent loop of the gastrojejunostomy. **Control group:** Patients after pylorus-preserving pancreaticoduodenectomy followed by Child reconstruction. **Follow-up:** The last study visit will take place at day 90 after the surgical treatment. **Length of intervention/Follow-up per patient:** 90 days postoperatively
Inclusion and exclusion criteria	**Inclusion criteria:** 1. Patients with benign or malignant diseases of the pancreas, the distal bile duct and the duodenum requiring a pylorus-preserving pancreaticoduodenectomy. 2. Surgical reconstruction by Child reconstruction defined as pancreaticojejunostomy followed by hepaticojejunostomy followed by gastrojejunostomy. 3. Age ≥ 18 years. 4. Ability to understand the character and individual consequences of the clinical study and to sign the informed consent. **Exclusion criteria:** 1. Patients undergoing classical Kausch-Whipple resection. 2. Patients undergoing pylorus-preserving pancreaticoduodenectomy with requirement of intraoperative arterial resection. 3. Patients with pylorus-preserving pancreaticoduodenectomy with requirement of multivisceral resections. 4. Distal pancreatectomy.

	5. Enucleations. 6. Patients after previous major GI-surgery in medical history. 7. Pregnant or breast-feeding women. 8. Planned re-laparotomy up to 30 days after initial surgery. 9. Emergency surgery.
Endpoints	**<u>Primary endpoint:</u>** Incidence of clinically relevant postoperative pancreatic fistulas (POPF) according to the current definition of the International Study group of Pancreatic Surgery (ISGPS) [1] within a postoperative period of 30 (+10) days (POD). **<u>Secondary endpoints</u>:** 1. Incidence and severity of clinically relevant postoperative delayed gastric emptying according to ISPGS-definition [2] (30 POD) 2. Incidence and severity of postoperative haemorrhages according to ISGPS-definition [3] (30 POD) 3. Incidence and severity of postoperative surgical complications according to the Clavien-Dindo classification within 30 days after surgery [4] 4. Complication comprehensive index [5] after operation during hospital stay 5. In-hospital, 30- and 90-day mortality rates 6. Incidence of reoperations and reinterventions due to POPF, delayed gastric emptying (DGE), post-op hemorrhage 7. Incidence of anastomotic leaks of the Braun enteroenterostomy 8. Quality of life after pancreas resection (EORTC QLQ-C30) 9. Length of hospital stay (measured between day 0 of the operation and discharge) 10. Length of stay on ICU (measured from day 0 of the operation) 11. Histopathological tumor stage 12. Postoperative pain assessment (pain at rest and pain during movement) according to the Visual Analogue Scale (VAS 0-10) 13. Incidence of re-admission within the duration of the study after discharge until Visit 5 (POD 30 + 10). **Assessment of safety:** Incidence of special interest (serious) adverse events.
Design of the study	Multicentre, prospective, randomized-controlled, observer-blinded study.
Amount of patients in each study arm	To be assessed for eligibility: n = 1000 To be assigned to the study: n = 606 To be analysed: n = 606

Time table:	I. Study planning phase: approx. 6 months II. First patient in (FPFV) to last patient out (LPLV): approx. 45 months III. Recruitment period: approx. 42 months IV. Study finalization including statistical evaluation, reporting and publication: approx. 9 months.
Number of centres	Approximately n= 18

III. Index

1. Introduction

1.1 Background: Clinically relevant postoperative pancreatic fistula and delayed gastric emptying after pancreas resection

Whereas 53,670 new cases of pancreatic cancer were estimated, nearly the same amount of deaths – namely 43,000 – were expected for 2017 in the USA [6]. For these patients the resection of the pancreas head remains the treatment of choice and the only possibility for curative therapy [7, 8]. Due to its anatomic position in the retroperitoneal space, the resection of the pancreatic head originally includes the resection of the pancreatic head itself, the resection of the ductus choledochus, of the gallbladder, of the duodenum and of the distal part of the stomach called Kausch-Whipple operation [9].

Importantly, mortality rates after pancreas head resections ranged between 20-40% for the following 50 years after first description of Whipple et al. in 1935 [9] and could be dropped below 5% in highly specialized centres [10-12] due to progress in surgical techniques and progress in critical care management. To reduce the high rates of postoperative mortality, several surgical reconstruction methods have been described. Here, even the seminal publication by Whipple did not describe a single, “standardized” surgical reconstruction technique, but included various two-staged reconstruction possibilities after pancreatoduodenectomy (PD) [13]. In 1944, Child published a broad series of reconstruction techniques after PD [14]. In this manuscript, Child and colleagues firstly described their modified gastrointestinal reconstruction after Whipple’s procedure by performing first the pancreaticojejunostomy followed by hepaticojejunosomty and duodenojejunostomy [14], which is called Child (standard Child reconstruction [s-Child]) reconstruction and is presently most widely used (Fig. 1a). Moreover, although described already in 1944 by Watson et al. [15], it was not until 1978 that the next modification of the surgical procedure was successfully introduced by Traverso and Longmire [16]. This reconstruction method preserved the pylorus of the stomach and a duodenojejunostomy instead of a gastrojejujnostomy was performed which is called pylorus-preserving pancreaticoduodenectomy, pylorus-preserving Whipple (PPPD) or Traverso-Longmire operation [16].

In contrast to mortality, the incidence of postoperative complications did not relevantly change within the last decades with morbidity rates reaching up to 60% [8]. Here, postoperative pancreatic fistulas (POPF) and delayed gastric emptying (DGE) belong to the most troublesome and feared postoperative complications after pancreas surgery. To assess the severity of DGE and POPF, the International Study Group of Pancreas Fistula (ISGPF) and the International Study Group of Pancreas Surgery (ISGPS) developed their classification systems of DGE and POPF depending on the clinical impact and the need for therapeutic

procedures [2, 17].

DGE is defined as a partial or total paralysis of the stomach leading to a prolonged stay of food in the stomach. Even though DGE also occurs in other upper GI-surgery such as gastrectomy or esophagectomy with vagotomy [18-23], DGE is especially common in patients undergoing pancreas resection with an incidence of nearly 50% [24-27]. Although DGE is not a life-threatening complication, DGE reduces quality of life in patients after pancreas surgery and leads to a prolonged hospital stay leading to increased costs [11, 28-30]. In contrast to DGE, POPF was less common in patients after pancreas resection. Here, the incidence for all kinds of POPF reaches up to approximately 20-30% and is approximately 10-20% for clinically relevant POPF Grade B/C [31, 32]. However, actual randomized controlled trials (RCT) even reported incidences of clinically relevant POPF exceeding 20% [32]. Importantly, whereas DGE does not affect overall survival of patients after pancreas resection, clinically relevant POPF grade B and C crucially increase the risk for postoperative mortality after pancreas resection up to nearly 20% [17, 33]. Besides mortality, clinically relevant POPF unfavourably affect the outcome of patients after pancreas resection. Here, Pratt et al. could show that the increasing degree of clinically relevant POPF also positively correlates with the clinical and economic impact on patients and with the decrease of their healthcare resources [34, 35]. Moreover, in their recent study, Williamsson et al. [36] could clearly demonstrate that the presence of POPF is strongly associated with increased serve complications defined as Clavien-Dindo >3 (no clinically relevant POPF 30/283 vs. clinically relevant POPF 23/39, $p<0.001$), an increased risk for stay in ICU (no clinically relevant POPF 21/283 vs. clinically relevant POPF 14/39, $p<0.001$), for DGE (no clinically relevant POPF 42/283 vs. clinically relevant POPF 24/39 $p<0.001$), for interventional radiology (no clinically relevant POPF 34/283 vs. clinically relevant POPF 18/39, $p<0.001$), for reoperations (no clinically relevant POPF 4/283 vs. clinically relevant POPF 4/39, $p<0.009$), increased hospital costs (no clinically relevant POPF 22,181€ vs. clinically relevant POPF 34,061€, $p<0.001$) and increased length of hospital stay (no clinically relevant POPF 12 days vs. clinically relevant POPF 27 days, $p<0.001$) [36]. Regarding these unfavourable impacts of DGE and of POPF on postoperative outcome, surgical and medical treatments reducing the incidence of DGE and POPF are on spotlight of current research.

1.2 Complications and risk factor of complications after pancreas resections

To reduce the incidence of POPF and DGE, several surgical techniques have been developed including PPPD and an additional enteroenterostomy between the afferent and the deferent loop of the duodenojejunostomy, which is called Braun enteroenterostomy or Braun anastomosis (BE) [37-41] (Fig. 1b).

To assess the impact of BE on the postoperative outcome of patients undergoing pancreas resection, Huang et al. performed a systematic review with meta-analysis in 2015 [40]. Here, an additional BE after pancreas resection showed a decreased incidence of DGE (odds ratio [OR] 0.30, 95% confidence interval [CI] 0.15-0.60; p=0.0007), of overall morbidity (OR 0.61; 95% CI 0.47-0.80; p=0.0003) and the length of hospital stay (LOS) (mean difference [MD] -1.80, 95% CI -3.4-(-)0.18; p=0.03). Moreover, no impact could be observed on the incidence of POPF Grade A/B/C (OR 0.70; 95% CI 0.35-1.40; p=0.31) whereas no stratification was performed according to their severity. Whereas this systematic review with meta-analysis was not able to identify any RCT, three RCT have been published since 2015 analysing the effect of BE on DGE after pancreas resection with s-Child [41-43]. Therefore, to get an actual overview of the impact of BE on POPF and DGE, we recently performed a systematic review with meta-analysis including also the published RCTs. Moreover, the ISGPS recently recommend to define POPF Grade A as biochemical leak and to include consequently only POPF Grade B and C in morbidity rates. However, using these recommendations we decided to include also a meta-analysis of clinically relevant POPF Grade B/C according to ISGPS [1] in our current systematic review. For this purpose, we screened actual literature in April 2017 for studies comparing s-Child against s-Child with an additional Braun enteroenterostomy (BE-Child) for the postoperative outcome of patients after open PD [44]. Although BE-Child did not affect the postoperative mortality (RR 0.75, 95% CI 0.35-1.63; p=0.47, I^2=0%) (Fig. 2a), we could clearly show that BE-Child strongly decreases overall morbidity (RR 0.75, 95% CI 0.65-0.88; p=0.0002, I^2=29%) (Fig. 2b) and length of hospital stay (LOS) (MD -1.37 days, 95% CI -2.77-0.03; p=0.05, I^2=0%) whereas BE-Child was associated with an increased operation time (MD 17.72 minutes, 95% CI 8.27-3.66; p=0.0002, I^2=0%) [44]. Moreover, no impact was detectable for the risk of haemorrhage (RR 1.18, 95% CI 0.71-1.97; p=0.52, I^2=0%), of surgical site infections (SSI) (RR 1.01, 95% CI 0.70-1.46; p=0.97, I^2=0%), of pulmonary infections (RR 0.96, 95% CI 0.60-1.53; p=0.85, I^2=45%) and of perioperative blood loss (MD 0.29 ml, 95% CI -0.02-0.61; p=0.06, I^2=78%)[44]. Strikingly, the effect of BE-Child becomes even more evident after screening actual literature on the impact of BE on pancreaticojejunostomy and hepaticojejunostomy. No or a slight risk reduction was visible for POPF Grade A/B/C (RR 0.90, 95% CI 0.75-1.08; p=0.27, I^2=0%) and for DGE Grade A/B/C (RR 0.77, 95% CI 0.59-1.01; p=0.06, I^2=53%), respectively [44]. In contrast, the incidence of clinically relevant POPF Grade B/C (POPF Grade B/C: RR 0.48, 95% CI 0.35-0.65; p<0.00001, I^2=46%) and clinically relevant DGE B/C (DGE Grade B/C: RR 0.43, 95% CI 0.22-0.86; p=0.002, I^2=74%) diminished in the presence of BE (Fig. 3a-b) [44]. Accordingly, also the incidence of insufficiencies of the hepaticojejunostomy declined in patients after pancreas resection and BE-Child (RR 0.52, 95% CI 0.31-0.87; p=0.01, I^2=0%) compared to patients with s-Child [44]. One explanation of these

findings is that the additional enteroenterostomy between the afferent and efferent loop of the duodenojejunostomy leads to a decreased stasis of gastrointestinal juice including pancreatic and biliary juice with a relief of the pancreaticojejunostomy and hepaticojejunostomy. This hypothesis is underlined by the findings of Wang et al. who reported that alkaline reflux gastritis and marginal ulcers were less present in patients after pancreas resection and BE-Child compared to patients with s-Child [45].

Although the meta-analysis provided strong indices of a protective effect of BE after Whipple's procedure, some limitations should be discussed. Here, only 3 RCTs could be identified and included in the analysis of BE-Child vs. s-Child's reconstruction whereas it was 3 prospective, randomized-controlled trials and 7 retrospective studies. However, even the included RCT had only a low power by including a maximum of 35 patients per study arm, which did not seem to be an adequate number to allow any statement of the true impact of BE on clinically relevant DGE or clinically relevant POPF. Moreover, our current systematic review with meta-analysis included patients with classical Whipple's procedure and PPPD. Although we planned to perform subgroup analysis stratifying patients into classical Whipple's procedure and PPPD, these subgroups included only a low number of patients with a consecutive low power.

As a consequence, regarding the high amount of patients included by retrospective studies, the low power of RCT and the heterogeneity of the cohorts including patients with classical Whipple's procedure and PPPD, the true impact of the BE after PPPD remains unanswered and a RCT with an adequate power is urgently needed.

2. Aim of the study

The Child reconstruction belongs to the routine GI reconstruction after PPPD. So far, only three RCT were performed which were published between 2015 and 2017. Participating centres were localized in Japan [42], in South Korea [41] and in Iran [43, 44]. Importantly, a RCT representing Caucasian in Europe is currently missing. Moreover, the number of participating patients of the different studies with a maximum number of 34 patients per study arm leads to the conclusion that the power of the published studies may be insufficient especially to predict its impact on clinically relevant POPF according to the new definition of ISGPS published in 2016 [1]. Therefore, the aim of the study is to assess the impact of BE-Child on postoperative outcome compared to s-Child reconstruction in patients undergoing PPPD in a multicentre, double-blinded, prospective, randomized controlled clinical study.

2.1 Design of the study

This clinical study is designed as a multicentre, randomized controlled, observer-blinded study with two study arms:

Group 1: Patients with pylorus-preserving pancreaticoduodenectomy and standard Child (s-Child) reconstruction (Fig. 1a)

Group 2: Patients with pylorus-preserving pancreaticoduodenectomy and Child reconstruction with Braun enteroenterostomy (BE-Child) (Fig. 1b)

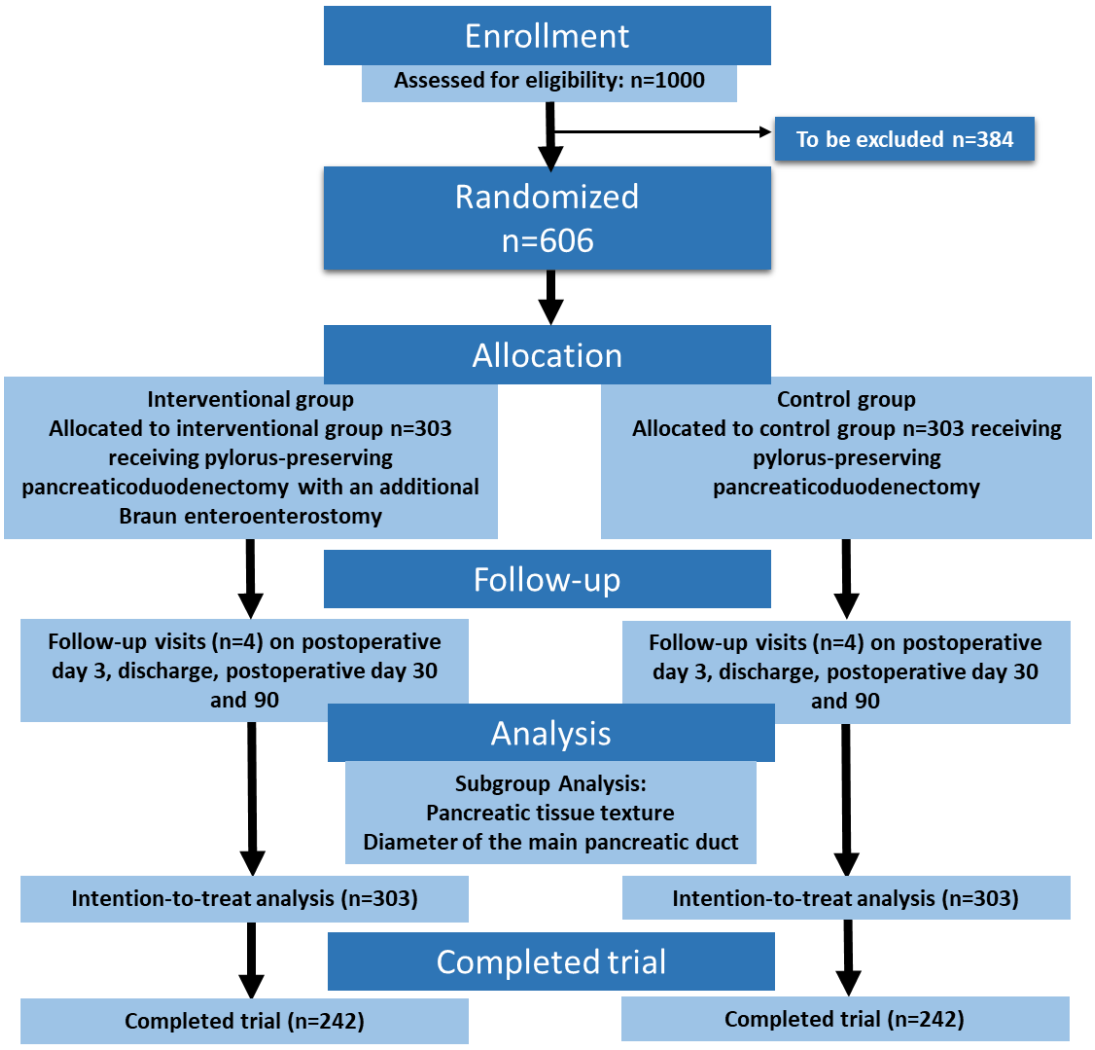


Figure 4. Schematic procedure of the current study of the impact of an additional BE in patients undergoing pylorus-preserving partial pancreatoduodenectomy.

2.2 Rationale of the primary endpoint

Postoperative complications in pancreas surgery could be observed in nearly 50% of all

patients with pancreas surgery [46]. Although severe complications were rare especially in highly specialized hospitals, also low and moderate grade postoperative complications harbour the risk that urgently needed postoperative treatment such as follow-up treatment or even adjuvant therapy in cancer patients may be delayed. POPF and DGE belong to the most troublesome and feared postoperative complications after pancreas surgery. To assess the severity of DGE and POPF, the International Study Group of Pancreas Surgery/ISGPS developed their classification systems of DGE and POPF depending on the clinical impact and the need for therapeutic procedures [2, 17]. In several further studies it could be shown that DGE and POPF were strongly associated with a decreased quality of life, increased postoperative severe complications (Clavien-Dindo >3), an increased risk for wound infections, a prolonged hospital stay leading to increasing costs or in cases of clinically relevant POPF even with an increased postoperative mortality [11, 28-30, 33, 36, 47].

Therefore, the aim of the study is to compare the incidence of clinically relevant POPF and clinical DGE according to ISGPF and ISPGS, respectively, in patients undergoing PPPD and receiving either BE-Child or s-Child reconstruction. Additionally, the incidence of AEs and SAEs of special interest as defined in chapter 8 of this clinical study protocol will be compared between the two study arms to provide a bright overview about the impact of BE on the postoperative course of patients with pancreas resection. Moreover, to provide a standardized definition of severity of postoperative complications and to allow an objective evaluation of AEs and SAEs, the comprehensive complication index was chosen to classify the severity of postoperative complications [5]. To ensure that readmissions and late postoperative surgical complications will be assessed for this clinical study, a study visit should be scheduled after discharge from the hospital on the POD 30 + 10, if possible. If this is not possible or the patient does not appear to the visit, there is the option of a telephone interview. These patients who will be evaluable for the primary endpoint (development of POPF B/C), the primary endpoint will be classified as “patients with POPF B/C” for the following study visits. Importantly, regardless of the primary endpoint, all patients will be followed up until POD 90+20 days to assess secondary endpoints.

2.3 Primary endpoint

Primary endpoint of this study is the incidence of clinically relevant POPF according to the actual definition of the ISGPS [1] within a **postoperative period of 30 (+10) days**. The checklist for POPF according to the recommendation of the ISGPS is provided as table 2 in the Appendix.

Moreover, in case of postoperative complications, the presence and/or a possible correlation of an increased amylase activity in drain fluids or abdominal fluid collections (if appropriate) to

minimize the risk for under- or overestimation of POPF and POPF-related complications will be captured.

2.4 Secondary endpoints

1. Incidence and severity of clinically relevant postoperative delayed gastric emptying according to ISPGS-definition [2] (30 POD)
2. Incidence and severity of postoperative haemorrhages according to ISGPS-definition [3] (30 POD)
3. Incidence and severity of postoperative surgical complications according to the Clavien-Dindo classification within 30 days after surgery [4]
4. Complication comprehensive index [4] after operation during hospital stay
5. In-hospital, 30- and 90-day mortality rates
6. Incidence of reoperations and reinterventions due to POPF, delayed gastric emptying (DGE), post-op hemorrhage
7. Incidence of anastomotic leaks of the Braun enteroenterostomy
8. Quality of life after pancreas resection (EORTC QLQ-C30)
9. Length of hospital stay (measured between day 0 of the operation and discharge days)
10. Length of stay on ICU (measured from day 0 of the operation)
11. Histopathological tumor stage
12. Postoperative pain assessment (pain at rest and pain during movement) according to the Visual Analogue Scale (VAS 0-10)
13. Incidence of re-admission within the duration of the study after discharge until Visit 5 (POD 30 + 10).

For DGE:

In accordance to POPF, only items of DGE according to the recommendations of the ISGPS (see Appendix Table 3) will be assessed by the study visits by each study centre.

For the comprehensive complication index:

Each postoperative surgical complication during the hospital stay in each patient will be assessed and graded according to the CDC[4]. The CCI will then be calculated as the sum of all complications[5].

Assessment of safety:

Incidence of special interest (serious) adverse events.

3. Organisational structure

3.1. Study leadership

Coordinating Investigator Prof. Dr. med. Daniel Reim	Technische Universität München Klinikum re. d. Isar Department of surgery Ismaningerstraße 22 81675 München
Applicant DFG and Investigator Dr. med. Stephan Schorn	

3.2 Statistics

Patrick Maisonneuve	Head, Unit of Clinical Epidemiology IEO, Istituto Europeo di Oncologia, IRCCS via Ripamonti 435 20141 Milan, Italy
Dr. rer. nat. Bernhard Haller Interim Analysis	Institut für KI und Informatik in der Medizin Ismaninger Straße 22 81675 München

3.3 Coordinating Centre for Clinical Studies

Organizational Project management, Monitoring, Data- and Safety-Management	Münchner Studienzentrum (MSZ) TUM, School of Medicine Ismaninger Straße 22 81675 Munich

3.4 Participating study centres

The current study is planned as a multicentre study with approx. 18 sites in Germany. Investigations and interventions which are part of this study will be performed by experienced physicians and study nurses. All information of the study centres including the investigators, and members of the study team will be recorded in a separate list.

3.6 Funding

The Investigator-initiated clinical study is kindly funded by the Deutsche Forschungsgemeinschaft (DFG) and granted under the number: SCHO1694/1-0.
In addition, the TUM, Klinikum rechts der Isar, i.e. the Department of Surgery kindly provides further support by basic equipment

4. Study details

4.1 General design and study flow

The clinical study is designed as a multicentre, randomized, controlled, observer-blinded parallel-group study (see also Fig. 4, schematic flow of procedures).

4.2 Study flow

Patients, who were planned to undergo PPPD, will be consecutively screened according to inclusion and exclusion criteria (Paragraph 4.5). After giving informed consent, patients will be included. To minimize dropouts of patients caused by intraoperative findings, *randomization* in a 1:1 ratio (Paragraph 7.3.) (in an interventional group of patients with BE-Child after PPPD or a control group of patients with s-Child after PPPD) will be performed at the end of the surgical procedure, which in each participating centre is performed according to local standards and the anatomical situation including a single loop reconstruction with a pancreaticojejunostomy, a hepaticojejunostomy and duodenojejunostomy in this predefined order for GI reconstruction. In case of randomization into the interventional arm (Group 2), an additional BE will be performed between the afferent and efferent loop of the duodenojejunostomy. Importantly, BE should be placed approx. 20cm distal of the duodenojejunostomy (afferent and efferent loop) and approx. 20-40 cm distal of the hepaticojejunostomy and should size 5-10cm. After surgery, four further visits will be performed as outlined in the study flow chart (Paragraph 5.6). In addition to the primary and secondary endpoints (Paragraph 2.3, 2.4), adverse events of special interest (Paragraph 8.3) will be documented. Figure 4 illustrates the schematic procedure of the study including screening, randomization and postoperative visits.

4.3 Time table

I. Study planning phase: approx. 6 months
II. First patient in (FPFV) to last patient out (LPLV): approx. 45 months
III. Recruitment period: approx. 42 months
IV. Study finalization including statistical evaluation, reporting and publication: approx. 9 months.

4.4 Discussion of the study design

The current study is a prospective, randomized-controlled, observer-blinded study with two different arms (Figure 4). The study aims to evaluate the clinical impact of BE in patients after PPPD on the occurrence of postoperative surgical complications. Here, pancreas resection, especially these due to pancreatic malignancies, harbours the risk that a pancreas head resection may not be feasible and that other surgical procedures have to be performed instead such as palliative drain procedures, palliative bypasses arterial or multivisceral resections. Therefore, to minimize the dropouts of patients, the inclusion and exclusion criteria will be critically re-evaluated during the operative procedure by each study team. Only after re-evaluation of the inclusion (all patients after PPPD and s-Child which is defined as a pancreaticojejunostomy, a hepaticojejunostomy and a duodenojejunostomy in this predefined

order (Figure 1a-b)) and exclusion criteria, and after performance of the last anastomosis, patients will be randomized either in the control group (no further surgery) or in the interventional group with an additional BE between the afferent and efferent loop of the duodenojejunostomy (Fig. 1b). For the postoperative visits, the commonly used classification of postoperative complications according to the CCI will be used as a standardized tool to assess the severity of postoperative complications[5]. Additionally, severity of POPF, DGE and of postoperative haemorrhages will be classified according to the ISGPS-criteria [1-3] in each patient. Importantly, most POPF grade A are asymptomatic and do not need any therapeutic procedures [1]. Accordingly, the new classification of POPF according to the ISPGS classify POPF grade A as biochemical POPF and does not recommend to include them in mortality rates. Therefore, regarding the recommendation of the ISGPS and the missing clinical impact of POPF grade A in postoperative outcome, only postoperative pancreatic fistula grade B and C will be evaluated and included in mortality rates in this study.

4.5 Blinding

At each study site, in addition to the not-blinded surgeon, there will be a blinded assessor who evaluates the outcome regarding the primary endpoint. Study patients are kept blinded as well. Unblinding is possible in case of emergency treatment.

4.6 Study Population and inclusion-/exclusion criteria

Study population are patients with a planned pylorus-preserving pancreaticoduodenectomy.

Inclusion criteria:

1. Patients with benign or malignant diseases of the pancreas, the distal bile duct and the duodenum requiring a pylorus-preserving pancreaticoduodenectomy
2. Surgical reconstruction by Child reconstruction defined as pancreaticojejunostomy followed by hepaticojejunostomy followed by gastrojejunostomy
3. Age ≥ 18 years.
4. Ability to understand the character and individual consequences of the clinical study and to sign the informed consent

Exclusion criteria:

1. Patients undergoing classical Kausch-Whipple resection
2. Patients undergoing pylorus-preserving pancreaticoduodenectomy with requirement of intraoperative arterial resection

3. Patients with pylorus-preserving pancreaticoduodenectomy with requirement of multivisceral resections
4. Distal pancreatectomy
5. Enucleations
6. Patients after previous major GI-surgery in medical history
7. Pregnant or breast-feeding women
8. Planned re-laparotomy up to 30 days after initial surgery
9. Emergency surgery

4.7 Subsequent exclusion of study participants

Study participants are able to withdraw their informed consent from this study at any time without giving any reason. All collected data of these patients may be evaluated until the time point of withdrawal of informed consent except patients wish a deletion of their data in written form.

The investigators are not allowed to exclude patients from the current clinical study, except in case of a potential hazard of life or healthiness or in case of noncompliance of these patients. All exclusions of patients and their reasons have to be documented in the study files including the date and the reason.

4.8 Premature termination of the study

The study leader is allowed to terminate the study because of medical or ethical reasons or because of infeasibility at any time point. In this case, the reason of the premature termination has to be recorded in detail and all efforts should be undertaken that included patients will undergo a final examination, which will be documented. Moreover, if an investigator has ethical doubts concerning this study, the study leader has to be informed about these doubts.

A premature termination of this study will occur if:

- the risk-benefit of the clinical study changes within the study
- the study leader has to terminate this trial because of safety reasons
- a clear advantage or a disadvantage of one arm will be detected during the clinical study, i.e. by intermediate data analysis
- study is not feasible

5. Flow Chart and study procedures

5.1 Visit 1/Day-28-(-)1: Screening and baseline

All patients with a planned PPPD within four weeks before surgical procedure will be screened

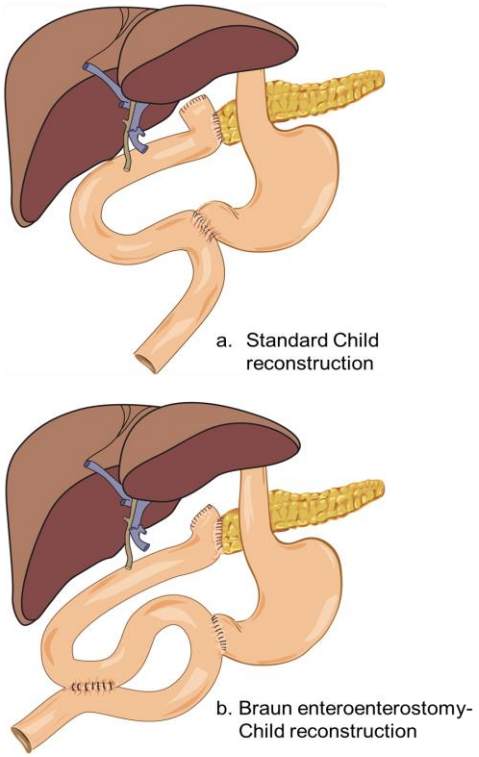
for inclusion and exclusion criteria and listed in the screening list. After explanation of the study and its procedures and after signing the informed consent, patients will be included into the study.

The further study procedure study can be found in chapter 5.7 and 5.8.

5.2 Visit 2/Day0: Operative procedure, intraoperative randomization

Figure 1: Surgical reconstruction methods after Whipple's procedure

Schorn et al., Fig. 1a-b:



Operative procedure, intraoperative randomization:

- Operation performed according to the local standard: PPPD followed by s-Child defined as single loop reconstruction with a pancreaticojejunostomy, a hepaticojejunostomy and a duodenojejunostomy in this predefined order (Fig. 1).
- Web-based randomization according to the procedure of randomizer.at to be performed at the end of the surgical procedure.

Interventional group:

Additional Braun enteroenterostomy: The BE should be placed approx. 20 cm proximal of the

duodenojejunostomy (afferent and efferent loop) and 20-30 cm distal of the hepaticojejunostomy and should measure approx. 5-10 cm in length. For further information about the exact randomization process, please see paragraph 7.3.

Control group:

No further intervention.

All patients should receive a passive, intraperitoneal drainage (Easyflow, Robinson or Jackson-Pratt), which should be removed according to institutional standard. For handling with drain and drain fluid, a SOP will be provided.

After wound closure, a sterile wound dressing will be performed. To minimize the risk of contamination of the surgical site during the operative procedure the wound edges should be covered with surgical dressings or with a sterile circular polyethylene drape and a change of the gloves before skin closure is recommended. GI reconstruction procedure is documented only for use in source data, documentation in eCRF is kept blinded. However, to enable further blinding, the patient and the investigator involved in postoperative assessments are kept blinded.

The further study procedure study can be found in chapter 5.7 and 5.8.

5.3 Visit 3/Day 5-6: Postoperative Visit

The first postoperative visit will be performed on POD 5-6.

The further study procedure study can be found in chapter 5.7 and 5.8.

5.4 Visit 4/Discharge: Discharge visit

Patients are discharged from hospital according to local standards and according to the clinical situation of the individual patient.

The further study procedure study can be found in chapter 5.7 and 5.8.

5.5 Visit 5/Day 30-40 Follow-up (Phone interview /On-site study visit)

Visit 5 can be done by telephone according to the prepared SOP or as regular study visit. This visit aims to detect late postoperative complications which may occur after discharge of patients. Therefore, patients will be asked for postoperative complications. If patient interview unsuccessful, patients´ treating physician are to be contacted for documentation.

The further study procedure study can be found in chapter 5.7 and 5.8.

5.6 Visit 6 Day 90-110

Visit 6 can be done by telephone according to the prepared SOP or as regular study visit. This visit aims to detect late postoperative mortality (Y/N) which may occur after discharge of patients.

The further study procedure study can be found in chapter 5.7. and 5.8.

5.7 Flow Chart

Study Procedures	Visit number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5*	Visit 6*
	Time of Visit (day)	Screening Baseline	OP day 0 Operation	POD 5-6	POD Discharge	POD 30 +10	POD 90 +20
Inclusion/Exclusion criteria		x					
Information & Informed consent		x					
Medical history[1]		x					
Clinicial examination [2]		x		x	x		
Demography [3]		x					
Quality of life EORTC QLQ-C30[4]		x			x	x	
Pain assessment VAS 0-10		x		x	x	x	
PRO-CTCAE[4]		x			x	x	
Operation [5]			x				
Intraoperative risk factor assessment [6]			x				
Randomization			x				
Prophylactic administration of somatostain analogues [7]				x	**Optional*** **		
Amylase activity in serum				x	**Optional*** **		
Maximum amylase level in drain fluid					x		
Assessment POPF according to table 2 (based on ISGPS) [8]					x	x** **Primary Endpoint**	
Grading of DGE table 3 (based on ISGPS) [9]					x	x**	
Grading of post-op hemorrhage according to table 4 (based on ISGPS) [10]					x	x**	
Histopathological tumor stage					x		
Postoperative complication [11]			x ****	x	x	x	
(S)AE of special interest			x****	x	x	x	
Phone interview [12]						x	x

*** Visits 5 and 6** can either take place via telephone or face-to-face in the hospital.
****** Grading table 2-4 takes place within the V5 at the end of the examination
*******Optional means that it must be entered in the eCRF when it is administered/done.
******** Recording of the AE and postoperative complication begins after surgery (stop date of the operation documented in the anesthesia protocol)

5.8 Footnotes for Schedule of Events:

1	**Medical history:** diagnosis, comorbidities, former GI-operations, ERCP with stenting before operationstent extraction before operation, Immusuppressiva,
2	**Clinicial examination:** vital signs (Blood pressure systolic (mmHg), Blood pressure diastolic (mmHg), , heart rate (bpm), temperature (°C), abdominal examination and clinical findings, pain assessment (VAS (0-10))
3	**Demography:** height (m), weight (kg), BMI (BMI additionally to **V5**), Age at inclusion, Sex, nicotine abuse
4	**Questionnaires:** patient reported outcomes according to **PRO-CTCAE and** Quality of life **(EORTC QLQ-C30)**
5	**Operation:** see Fig.1 - passive intraperitoneal drainage, intraoperative procedures - Surgical reconstruction was performed according to randomization Lymphadenectomy - Type of pancreaticojejunostomy [Cattell-Warren-Anastomosis vs. Blumgart-Anastomosis vs. other (specify)] - Partial portal venous resection - Type of surgical procedure (open vs. minimally-invasive vs. conversion from minimally-invasive to open) - Type of bile duct anastomosis (single layered vs. double layered) - Additional resections not usually included in PPPD - Placement of nasogastric tube (Y/N)
6	**Intraoperative risk factor assessment:** - Pancreatic texture (assessed by palpation as soft or hard) - Pancreatic duct diameter (<3mm or >= 3mm) - Operation time (skin incision to end of skin closure) - Estimated intraoperative blood loss in ml (refer to the anaesthesiologist's protocol) - Units of intraoperatively transfused red cell concentrates - Surgeon expertise(PD per year (1-10/10-20/>20) and years of experience in pancreatic surgery (1-5/>5))
7	**Administration of somatostatin analogues:** - Prophylactic according to local routine onsite
8	**Assessment POPF according to table 2 (based on ISGPS):** - Abdominal drain in place? (Reinsertion required if No: removed postoperative day) - Maximum amylase level in drain betweenVisit 3 and Visit 4 - Increased amylase activity > 3 times upper limit of institutional serum amylase level/clinical evidence of POPF if Yes: which treatment?: - None, observation - Overall time of drain: > 3 weeks - Therapeutic administration of somatostatin analogues (Y/N) - Enteral nutrition Y/N - Parenteral nutrition Y/N - PRBC Transfusion Y/N, (If Y: Units) - Re-intervention required?(If Y: interventional, endoscopic, angiographic) - Reoperation due to POPF Y/N - Infection signs related to POPF (without organ failure) - Infection signs related to POPF with organ failure (Reintubation, hemodialysis, Inotropic agents, other) - Death due to POPF - Prolongation hospital stay

	- ICU Treatment required - Other medications - Assessment of POPF: None/A/B/C
9	**Grading of DGE table 3 (based on ISGPS):** delayed gastric emptying: - Nasogastric tube (NGT) in place Y/N? Reinsertion required Y/N (If Y: postop day: ≤POD 3, POD 4-7, POD 8-14, ≥15 POD) - Overall time of NGT: 4-7 days, 8-13 days, ≥14 days - Vomiting/gastric distension after liquid/food intake (Y/N) - Unable to tolerate solid oral intake by POD 7/POD14/POD21 (Y/N) - Clinical Suspicion/Evidence of DGE - If Y: Diagnostics: Radiology (Y/N), Endoscopy (Y/N), Other - If Y: Therapeutic: Prokinetics (Y/N)? Parenteral Nutrition(Y/N? - If Y: Re-intervention, re-operation - If Y: Prolonged Hospital Stay? (Y/N), If Y: Hospital Stay (days) - Delay of adjuvant therapy (Y/N) - Grading of DGE according to ISGPS (see Table 3 A/B/C)
10	**Grading of post-op hemorrhage according to table 4 (based on ISGPS):** - Evidence of postoperative haemorrhage (Y/N) - If Y: Bleeding ≤24 h (early) or >24h (late) after the end of the index operation - Location: Intraluminal or extraluminal - Hb loss: >3 g/dl (severe bleeding) or <3g/dl (mild bleeding) - Diagnostic consequence: observation, blood count, ultrasonographie, computed tomography, angiography, endoscopy, other - Therapeutic cosequence: Transfusion of fluid/blood, therapeutic endoscopy, embolization, relaparotomy, angiography, localization of bleeding, intermediate care unit (or ICU), ICU, others - Clinical condition - Reintervention (angiographic intervention, endoscopic intervention) - Re-operation (relaparotomy) - Grading of postoperative haemorrhage: A/B/C
11	**Postoperative complication:** Incidence (n) and severity of postoperative surgical complications according to the Clavien-Dindo classification after surgery. Complication comprehensive index [5]**(CCI)** after surgery **Table 5** $\mathbf{CCI^{®}} = \frac{\sqrt{(wC_1 + wC_2 ... + wC_x)}}{2}$
12	**Phone interview:** Mortality

6. Ethical aspects

6.1 Independent ethics committees

The clinical study will be initiated at each study site after receiving an agreement of the respective ethics committee on its conduct.

6.2 Ethical performance of the study

The clinical study will be performed in accordance with the declaration of Helsinki of the World Health Organization (actual version Fortaleza, Brazil, October 2013) and according to

applicable national laws and regulations. Moreover, conception of the study protocol as well as study conduct will be performed according to Good Scientific Practice. Each ethics committees will be immediately informed in cases of changes of the study protocol, which impair patients' safety.
Additionally, substantial changes of the study protocol are submitted to the Ethics Committee for approval and will only be implemented after their approval.

6.3 Safety Monitoring Board

A Safety Monitoring Board (SMB) will be established for this clinical study including a statistician and a surgeon and gastroenterologist experienced in clinical research and in pancreatology. Safety data as outlined in chapter 8 will be sent to the SMB at least once every 6-12 months and, in addition, the SMB will be informed about the results of the interim analysis. The members of the SMB then report the result of the benefit/risk assessment to the study leader and will give appropriate recommendations concerning the study continuation. In case of any irregularities including frequencies or type of (S)AEs of special interest reported (see chapter 8), the study leader will inform the members of the SMB without delay.

6.4 Benefit-Risk-Analysis

The current study protocol follows clinical routine procedures and does not include any additional examinations, interventions or stress for the patient. Several other studies including RCTs and meta-analysis could not detect any increased risks for postoperative mortality or morbidity which were associated with the additional BE. In the contrary, several studies even reported that the presence of the BE is associated with a decreased risk for postoperative complications including clinically relevant DGE and POPF, which already led to the adoption of BE as a standard procedure by surgeons. Besides the routine procedures, patients will be asked to complete two questionnaires and will be asked for their pain assessment. Therefore, it seems plausible that the risk for patients is not increased by participating in this study.

6.5 Registration

Before inclusion of the first patient the study will be registered in a study register, which is accepted by the WHO (http://www.who.int/ictrp/en/; e.g. clinicaltrials.gov) including a statement about data sharing (Data Sharing Plan).

6.6 Informed consent and patients‘ agreement

A patient can only be included into the clinical study after having obtained provided his/her written informed consent. For this purpose, each patient has to be informed by an investigator

about the significance and the scope of the clinical study in an appropriate and understandable manner. Each patient has to be informed that he/she is allowed to withdraw their informed consent at any time without receiving any reprisals or disadvantages. Moreover, all included patients have to agree that data, which will be recorded and collected during this clinical study, may be presented to others delegated by the study leadership e.g. to monitor the study. The original of the informed consent form (ICF) will be stored at the study site. Patients will receive another original written informed consent. Study information and the informed consent will be submitted to the ethics committee for approval.

6.7 Data Privacy Protection and Confidentiality protection

The applicable local regulations on data privacy protection will be followed. The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The patients will be informed that any patient-related data and materials will be appropriately made pseudonymous and that these data may be used for analysis and publication purposes. Furthermore, the patients will be informed that their data may be checked by monitor/auditor for the purpose of validation of a proper conduct of the study. Patients who do not provide consent for transmission of their data, according to the data protection agreement included in the ICF, will not be included in the study. In the event of violations of the data security regulations, measures will be taken in accordance with the regulation(s) to limit potential negative effects.

7. Statistical methods

7.1 Number of patients

Based on the results of our current meta-analysis, an incidence of clinically relevant POPF of 22% could be assumed after PD. This incidence is in line with an actual RCT of 18 German high-volume academic centres for pancreatic surgery comparing the effect of pancreaticojejunostomy vs. pancreaticogastrostomy [48]. Thus, regarding the results of our current meta-analysis, a moderate clinical relevant effect of BE-Child could be assumed with an odds ratio of 0.5.

Study sample size is calculated using a two-sided Z test in a group-sequential design, with a single interim analysis after half of the patients have been enrolled.

Sample sizes of 242 patients in group 1 and 242 in group 2 achieve 80% power to detect a difference of 0.10 between the group proportions of 0.22 and 0.12 (corresponding to an OR=0.50) at a significance level (alpha) of 0.05 using a two-sided test. To account for 20%

loss of follow-up before the primary endpoint can be evaluated, a total of 606 patients (303 in each group) will be randomized.

7.2 Statistical analysis

7.2.1 Statistical study populations:

Intention-to-treat Population (ITT):

The primary and secondary endpoints will be analysed on the Intention-To-Treat set (ITT), consisting of all patients included in the study in the treatment arm they were randomized to. The safety analysis will be performed on the safety set, consisting of all patients randomized into the study, assigned to the treatment group of their actual treatment. We plan one interim analysis after 303 (50%) patients assuming a maximum 20% patients with missing information of primary endpoints. According to the O'Brien-Fleming Boundaries, the addition of BE will be declared beneficial and the trial could be successfully stopped prematurely when the p-value at interim analysis is $p<0.003$. At the end of the trial the incidence of clinically relevant POPF will be assessed in each group and compared using the O'Brien-Fleming Boundaries with an alpha of 5%. The tests will be performed two-sided with a global significance level of 5%. Secondary endpoints will be analyzed on the ITT set using appropriate descriptive statistics by study group. Any explorative statistical testing will be performed using a significance level of 5%. All AEs of special interest other than POPF will be analysed with incidence rates by treatment group and according to severity. AEs of special interest rated as related to the study treatment will be listed separately.

Supportive analysis of the primary endpoint: Supportive analysis of the primary endpoint will be performed using a binary logistic regression model including duration of operation, blood loss, diameter of the main pancreatic duct, pancreas tissue texture, surgeon's experience and patient related risk factors including BMI and diabetes.

Missing data: A multiple imputation procedure based on a logistic regression model will be performed to impute missing values in the primary outcome variable. Patients with missing information of the primary endpoint of less than 20% is expected in this study as all but two study visits will be performed during hospital stay and the last two study visits on POD 30 +10 days and on POD 90 +20 days are allowed to be performed as phone call. If a patient is lost to follow-up before the primary endpoint can be evaluated (no clinically relevant POPF reported during follow-up available), the risk for developing a POPF will be estimated for each patient. Multiple datasets with occurrence of POPF sampled for individuals with missing data in the primary outcome variable based on their estimated event probabilities will be generated. For the primary analysis, results obtained in those datasets will be aggregated. Importantly, to

allow an adequate risk estimation, perioperative data including estimated blood loss, length of operation, pancreatic tissue texture, main pancreatic duct size, experience of the surgeon and amylase activity of the drain fluid (if available) will be recorded for each patient.

Per-Protocol Population:

This study population includes all patients who will be included in the ITT and will be treated according to the protocol ("as treated"). Patients who will not be able to complete visit 5 except for death of the patients will also be excluded from per-protocol-analysis.

7.2.2 Evaluation of the primary endpoint

The evaluation of the primary endpoint will be performed in the intention-to-treat population (ITT) (see paragraph 7.2.1). The statistic hypothesis is:

$$H_0 : \Pi_T = \Pi_C \quad vs. \quad H_A : \Pi_T \neq \Pi_C .$$

Here, Π_T represents the incidence of POPF in the intervention group whereas Π_C is the incidence of POPF in the control group.

The incidence of POPF will be compared between the two groups by a multivariable, logistic regression model. Significance level will be fixed at 5%.

7.2.4 Subgroup analysis

The following subgroup analysis will be performed for the incidence and the severity of postoperative complications will be analyzed:

1) Texture of the pancreas (soft vs. hard)
2) Diameter of the main pancreatic duct
3) Benign disease vs. malignant disease
4) ASA Grad (1 und 2 vs. 3 vs. ≥4)
5) Biliary stenting (yes vs. no)

   The following parameters are used to define this subgroup:

   ERCP with stenting before operation (Y/N)

   Stent extraction before operation (Y/N)

6) Age (≤ 65 vs. >65)
7) Low-volume vs. high-volume recruiting centres
8) Minimally invasive vs. open PPPD

7.2.5 Secondary endpoints

All secondary endpoints will be presented with appropriate descriptive statistics per study group and be compared by using appropriate statistical tests. The Chi2 test and, if necessary, the Fisher Exact Test are used to compare frequencies between the groups. As required, t-

tests and Mann-Whitney U tests are used to compare groups with quantitative data. All statistical tests are carried out on both sides p-value with a significance level of 5%.

7.2.6 Safety analysis

For safety analysis, all AEs and SAEs of special interest (see Section 8) will be analyzed by descriptive statistics elaborating the frequency of AEs and SAEs in both groups. The Chi2 test and, if necessary, the Fisher Exact Test are used to compare frequencies between the groups. Patients who have started Visit 2 will be analyzed as "treated". AEs of patients who have received an unplanned intervention such as drain or palliative surgical procedure and consequently not randomized will be listed separately.

7.3 Randomization and “blinding” method

In order to ensure equal distribution of patient and cohort characteristics, randomization for treatment allocation will be applied. Allocation of treatments will be performed by using a web-based randomization tool (www.randomizer.at). Randomization will be performed stratified by centre and by texture of the pancreatic tissue. For the stratified randomization, the surgeon will assess the pancreatic tissue texture right before randomization and classify the texture “soft” or “hard”. Afterwards, a randomization into a control and an interventional arm will be performed within each stratum to ensure an equal distribution of the pancreatic tissue texture in the operating room. Basic characteristics of the patient and day of randomization must be documented. Subsequently, printed randomization sheets must be dated, signed and stored apart from the patient records, study documents and investigator site file to ensure blinding. Patients, outcome assessors and the study statistician will be blinded for the study intervention. The outcome assessor of the study centre will therefore neither be part of the surgical team nor have access to the printed randomization sheets. The report of the surgeon will only include the information whether the operation was performed as randomized or not. Patient and assessor will be blinded until the end of the study. In cases of emergency, blinding can be redrawn by information of the local study centre. Moreover, to guarantee blinding of the study statistician, the interim analysis will be performed at the Institute for Institut für KI und Informatik in der Medizin . In contrast to the interim analyses, the final study analysis will be performed at the European Institute of Oncology. By separating interim analysis and final study analysis the blinding of the study statistician will be guaranteed.

Importantly, as the occurrence of clinically relevant POPF should be regarded as a multifactorial event, we decided to perform subgroup analyses for the most relevant risk factors. Here, texture of the pancreatic tissue (soft vs. hard) and diameter of the main pancreatic duct (<3mm vs. ≥3mm) belong to the most well known risk factors for its occurrence.

Accordingly, subgroup analyses will be performed depending on the texture of the pancreas and on the main pancreatic duct diameter.

8. Study-specific risks

8.1 Definition of Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a study patient. An AE can therefore be any unfavourable and unintended symptom or disease temporally associated with the study intervention, whether or not considered related to the intervention.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.) The documentation of AEs in this study begins with visit 2 after surgery (stop date of the operation documented in the anesthesia protocol) and is limited to AEs of special interest (see chapter 8.3).

8.2 Assessment of Adverse Events

The intensity of adverse events of special interest will be graded using Common Terminology Criteria for Adverse Events (CTCAE) for Adverse Events Version 5.0.

8.3. (S)AEs of special interest

The following (S)AEs are of particular interest in this study and are captured in the eCRF (Please note that the (S)AE'S must also be documented in the eCRF by re-admission):

- Clinically relevant POPF according to the actual definition of the ISGPS
- Clinically relevant postoperative delayed gastric emptying according to ISPGS definition (DGE)
- Postoperative haemorrhages according to ISGPS-definition
- Postoperative surgical complications within 30 days after surgery
- wound healing disorder
- Anastomotic leaks / Bile leaks / Insufficiency of the Braun enteroenterostomy
- Adverse Events requiring l re-admission within the duration of the study after discharge
- Mechanical ileus
- Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study intervention

- steatorrhoe
- refractory diarrhea
- blood sugar imbalance

9. Data collection, Data Management, Monitoring, Publication, Archiving

9.1 Data collection

The documentation of the study data is the responsibility of the investigator. Original data (source documents) remain in hospital. Medical record and information on the eCRF must be traceable and consistent with the original data. Source documents are e.g. laboratory results. No information in source documents about the identity of the patients will be disclosed. All data collected in this clinical study must be entered in an eCRF which has to be completed by the investigator or authorized study personnel and signed by the investigator. This also applies for those patients who do not complete the study. In case of premature discontinuation, the reason must be recorded on the eCRF. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of all data reported to the study leadership in the eCRFs and in all required reports. After database lock, the investigator will receive the data of the study site.

9.2 Data Management

Data are programmed and processed by data management of the MSZ with the support of a study database (eCRF) taking into account on the SOPs of the MSZ.
A description of the study specific processes is given in the data management plan that details the key planning and control elements for the data management component of the study.
The evaluation of the data takes place by programmed validity- and consistency checks. In addition a manual/visual evaluation of plausibility is performed. Queries may occur, which will generally be visualized on the study database. The investigator has to resolve all data discrepancies in the study database.
After entry of all collected data and clarification of queries, the database will be closed at the completion of the clinical study.
Data and results electronically recorded will be archived according to legal guidelines.

9.3 Monitoring

Monitoring activities are performed to ensure that the clinical study is conducted in accordance with the study protocol. A monitoring plan describing the scope of the monitoring activities in detail will be prepared.
The responsible monitor will contact the investigator and will be allowed, on request, to inspect

the various records of the study (e.g. source data and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements. The monitor should have access to patient records, any information needed to verify the entries in the eCRF and all necessary information and essential study documents. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. A monitoring visit report is prepared for each visit describing the progress of the clinical study and all identified problems.

9.4 Publication

The study protocol and the study results will be published in a peer-reviewed journal. according to the CONSORT statement [49]. In addition, study results will be made available to public journals and platforms.

9.5 Archiving

At the end of the clinical study all study-relevant documents (e.g. ISF), data and records will be archived in accordance with legal requirements.

10. Abbreviations

95% CI	95% confidence interval
AE	Adverse events
BE	Braun enteroenterostomy
BE-Child	Child reconstruction with additional Braun enteroenterostomy
BMI	Body-Mass Index
DFG	Deutsche Forschungsgemeinschaft/German Research Foundation
DGE	Delayed gastric emptying
eCRF	Electronic Case Report Form
GI	Gastrointestinal
ICU	Intensive care unit
ISGPS	International Study Group of Pancreatic Surgery
ITT	Intention to treat
LOS	Length of stay
MD	Mean difference
MSZ	Münchner Studienzentrum/Munich Study Centre
NGT	Nasogastric tube
OR	Odds ratio
PD	Pancreatoduodenectomy
POD	Postoperative day
POPF	Postoperative pancreatic fistulas
PPH	Postpancreatectomy haemorrhage
PPPD	Pylorus-preserving partial pancreatoduodenectomy
RCT	Randomized controlled trial
RR	Risk ratio
s-Child	Standard Child reconstruction
SMB	Safety Monitoring Board
SOP	Standard Operating Procedure
T.E.N	Total enteral nutrition
T.P.N.	Total parenteral nutrition
TUM	Technische Universität München/Technical University of Munich
WHO	World Health Organization

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Schorn et al., Figure 2a-b:

a. BE-Child reconstruction does not affect mortality after pancreas resection

b. BE-Child reconstruction reduces morbidity after pancreas resection

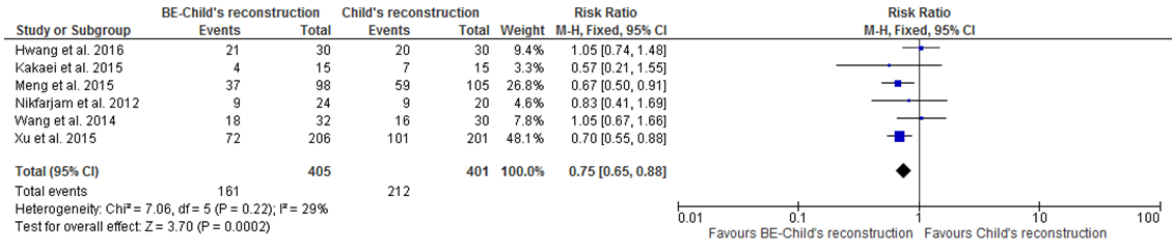
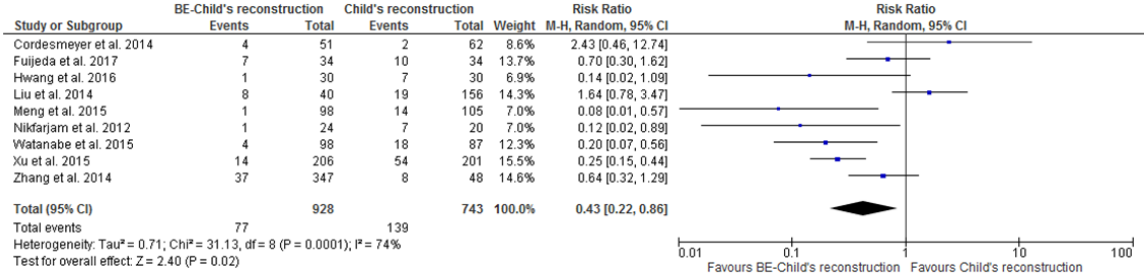


Figure 2: BE-Child (is associated with a decreased risk for overall morbidity but not for overall mortality compared to s-Child

Schorn et al., Figure 3a-b:

a. BE-Child reconstruction reduces clinically relevant DGE Grade B/C after pancreas resection



b. BE-Child reconstruction reduces clinically relevant POPF Grade B/C after pancreas resection

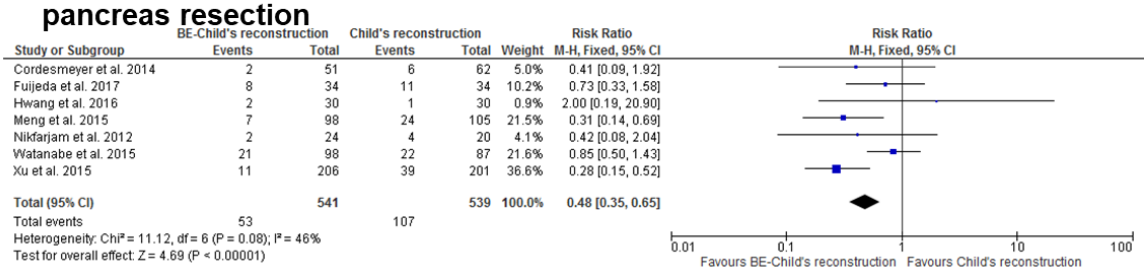


Figure 3: BE-Child is associated with a decreased risk for clinically relevant DGE and POPF compared to s-Child

Table 2: Severity of postoperative pancreatic fistula according to the International Study Group of Pancreatic Surgery [1]

Event	Biochemical leak	Grade B POPF	Grade C POPF
Increased amylase activity > 3 times upper limit of institutional normal serum value	**Yes**	**Yes**	**Yes**
Persisting pancreatic drainage >3 weeks	**No**	**Yes**	**Yes**
Clinically relevant change in management of POPF[1]	**No**	**Yes**	**Yes**
POPF percutaneous or endoscopic specific interventions for collections	**No**	**Yes**	**Yes**
Angiographic procedures of POPF related bleeding	**No**	**Yes**	**Yes**
Reoperation for POPF	**No**	**No**	**Yes**
Signs of infection related to POPF without organ failure	**No**	**Yes**	**No**
Sings of infection related to POPF with organ failure	**No**	**No**	**Yes**
POPF related organ failure[2]	**No**	**No**	**Yes**
POPF related death	**No**	**No**	**Yes**

1 Defined as prolongation of hospital or ICU stay or the use of therapeutic agents specifically employed for POPF management or its consequences (of these: somatostatin analogues, TPN/TEN, blood product transfusion or other medications).

2 Defined as the need for re-intubation, hemodialysis, and/or inotropic agents > 24 hours for respiratory, renal, or cardiac insufficiency, respectively.

Table 3: Severity of delayed gastric emptying according to the International Study Group of Pancreatic Surgery [2]

Event	Grade A	Grade B	Grade C
Naso-Gastric Tube/NGT required	4–7 days or reinsertion after POD 3	8–13 days or reinsertion after POD 7	≥14 days or reinsertion after POD 14
Unable to tolerate solid oral intake by POD	7	14	21
Vomiting/gastric distension after liquid/food intake	+/-	+	+
Nutritional support (enteral or parenteral)	Possibly yes (slower return to solid food intake)	Yes (partial parenteral nutrition)	Yes (total parenteral or enteral nutrition via NGT, prolonged, i.e., 3 weeks postoperatively)
DGE-specific treatment	Possibly yes (prokinetic drugs, potential reinsertion of NGT)	Yes (prokinetic drugs, potential reinsertion of NGT)	Yes (prokinetic drugs, NGT)
Diagnostic evaluation	No	Possibly yes (endoscopy, upper GI contrast study, CT)	Yes (endoscopy, upper GI contrast study, CT)
Interventional treatment	No	No	Possibly yes (e.g., abscess drainage, relaparotomy for complication, relaparotomy for DGE)
Prolongation of hospital stay	Possibly yes	Yes	Yes
Delay of potential adjuvant therapy	No	No	Yes

Table 4: Classification system of postpancreatectomy hemorrhage according to the International Study Group of Pancreatic Surgery [3]

Grade	Early postoperative bleeding, condition	Late postoperative bleeding, condition	Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early, intra- or extraluminal, mild	-	Well	Observation, blood count, ultrasonography and, if necessary, computed tomography	No
B	Early, intra- or extraluminal, severe	Intra- or extraluminal, mild*	Often well/ intermediate, very rarely life-threatening	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy†	Transfusion of fluid/ blood, intermediate care unit (or ICU), therapeutic endoscopy,† embolization, relaparotomy for early PPH
C	-	Late, intra- or extraluminal, severe	Severely impaired, life-threatening	Angiography, computed tomography, endoscopy[1]	Localization of bleeding, angiography and embolization, (endoscopy[1]) or relaparotomy, ICU

† Endoscopy should be performed when signs of intraluminal bleeding are present (melena, hematemesis, or blood loss via nasogastric tube).

Table 5: Clavien Dindo classification of surgical complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade III	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.
	*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

CCI® postoperative Komplikationsbewertung nach Clavien-Dindo-Klassifikation Bewertung der Gesamtmorbidität von Patienten anhand des Comprehensive Complication Index (CCI®)

$$\mathbf{CCI^{®}} = \frac{\sqrt{(wC_1 + wC_2 \ldots + wC_x)}}{2}$$

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