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Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial

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Abstract

Background:
Pancreatic fistula (POPF) remains the most common and serious complication after distal pancreatectomy. Many attempts at lowering fistula rates have led to unrewarding insignificant results as still up to 30% of the patients suffer from clinically relevant POPF. Therefore, the development of new innovative methods and procedures are still a cornerstone of current surgical research.
The CUSA device is a well-known ultrasound-based parenchyma transection method, often used in liver- and neurosurgery which has not yet been thoroughly investigated in pancreatic surgery, but first results seem very promising.

Methods:
The CUSA-1 trial is a randomized controlled pilot trial with two parallel study groups. This single-center trial is assessor and patient-blinded. A total of 60 patients with an indication for open distal pancreatectomy will be intraoperatively randomized after informed consent. The patients will be randomly assigned to either the control group with conventional pancreas transection (scalpel or stapler) or the experimental group, with transection using the CUSA device. The primary safety endpoint of this trial will be postoperative complications ≥ grade 3 according to the Clavien-Dindo classification. The primary endpoint to investigate the effect will be the rate of POPF within 30 days postoperatively according to the ISGPS definition. Further perioperative outcomes, including post-pancreatectomy hemorrhage (PPH), length of hospital stay and mortality will be analyzed as secondary endpoints.

Discussion:
Based on literature data, CUSA may have a benefitable effect on POPF occurrence. The rationale of the CUSA-1 pilot trial is to investigate the safety of the CUSA device and the effect on POPF occurrence in pancreatic surgery during elective open distal pancreatectomy compared to conventional dissection methods. This data will lay the groundwork for a future confirmatory multi-center randomized controlled trial.

Ethics and dissemination:
The CUSA-1 trial protocol was approved by the ethics committee of the University of Heidelberg (No. S-098/2022). Results will be published in an international peer-reviewed journal and summaries will be provided in lay language to study participants and their relatives.

Trial registration: German Clinical Trials Register (DRKS) DRKS00027474

Strengths and limitations of this study

- The CUSA-1 pilot trial is the first randomized controlled trial (RCT) that compares the application of the CUSA device with conventional dissection methods for pancreas transection in distal pancreatectomy patients investigating the occurrences of postoperative pancreatic fistulas (POPF).
- This trial will provide information about the safety of the CUSA device in pancreatic surgery and the effect on POPF occurrence. Based on this data, a future confirmatory multi-center RCT will be designed.
- The CUSA transection method may decrease POPF rate, which is still the most common and dangerous complication after partial pancreatectomy, having a significant impact on the postoperative course of the patients.

Background

Pancreatic surgery is a large and challenging field with approximately 10.000 annual partial pancreatectomies in Germany[1]. As the incidence of pancreatic cancer and therefore number of surgical interventions increases worldwide[2], the intra- and perioperative conditions have been continuously improved through further developments and standardization of processes[3-5]. The combination of increasing disease rates and thus complex pancreatic interventions with a considerable risk for complications still leads to a significant medical burden on the health care system[6, 7]. Postoperative pancreatic fistulas (POPF) are the most common and most serious complications after pancreatic surgery[8]. With an incidence varying from 10-15% for partial pancreatoduodenectomy and 20-30% for distal pancreatectomy according to the ISGPS-classification[9-12], the occurrence of POPF can decisively impair a patient's clinical course, as it may lead to further serious complications such as post-pancreatectomy hemorrhage (PPH), infections and even death in up to 33% in high risk populations[8, 13-15].

Many strategies and operative techniques have already been investigated with the aim of reducing POPF rates. A distinction regarding the different approaches can be made between remnant closure, pharmacological approaches, and the transection method itself. Several types of sealants for the pancreatic remnant after resection, such as fibrin glue or hemostyptics have been tested without desired results[16] Also, for mesh-augmentation no relevant efficacy could be measured[17]. The application of somatostatin analogues also failed to significantly reduce the rate of POPF development[18, 19]. The recently developed intraoperative pancreatic leakage indicator "SmartPAN", a device for the immediate detection of pancreatic leakages, is currently being investigated[20].

In addition to the above-mentioned methods, which mainly set after the transection process to seal the remaining pancreas, the third approach is to optimize the transection method itself. Up to date, the stapler or scalpel transection are the most common methods applied worldwide[15, 21]. However, the serious issue of POPF complication remains unsolved, and innovative methods for its prevention still need to be explored with high urgency.

In clinical routine, the CUSA device is frequently used in liver- and neurosurgery. It triggers tissue fragmentation depending on water concentration - tissue with higher water content (parenchyma) is fragmented faster than structures with a higher tissue content (vessels, duct structures). The tissue is then aspirated through the CUSA device exposing remaining duct and vessel structures, which can then be selectively ligated[22-24].

In as early as 1999, Suzuki et al. conducted a small RCT investigating the use of the Cavitron Ultrasonic Surgical Aspirator (CUSA, Integra lifesciences Corporation, NJ, USA) in comparison to conventional pancreas transection with scalpel in 27 (CUSA group) versus 31 (control group) patients undergoing distal pancreatectomy. The trial revealed a significantly lower POPF rate in the CUSA group (3.7% vs 25.8%, p=0.02)[25]. Despite these astonishing results, until now, no new RCTs were conducted on this approach. The rationale behind this finding might be the very precise tissue transection process when using the CUSA, so that even smallest pancreatic duct structures can be identified and sealed which possibly reduces the risk of POPF development. While CUSA was associated with a slightly longer transection time (23 vs 9 minutes), up to 30 tubular structures on the resection plane per patient were recognized including up to 6 pancreatic ducts each, which could then all be individually closed.

Unfortunately, in this trial, the patient population was very diverse and consisted of mainly locally advanced gastric cancer patients. In addition, only patients with non-fibrotic pancreatic parenchyma without main duct dilatation were included. Therefore, the internal and external study validity and especially transferability to patients with primary pancreatic lesions located in the body or tail are to some extent limited.

As the rationale and results of the above-mentioned trial are very promising and may have a substantial impact on the future of pancreatic surgery, it is our aim to investigate the CUSA method in an RCT in patients undergoing distal pancreatectomy for benign or malignant pancreatic pathologies. This will be the first pilot RCT with this patient population to investigate the CUSA transection technique with regard to POPF development.

Study design

Objective
The CUSA-1 trial investigates the safety and feasibility of the CUSA device in elective open distal pancreatectomy. This approach for pancreas transection will be compared with the conventional transection methods with scalpel or stapler. Data concerning safety and the effect on POPF occurrence as well as overall postoperative complications will be assessed. This study corresponds to a stage 2b investigation according to the IDEAL framework[26] and collects prospective data regarding safety and feasibility parameters in an exploratory character with the aim of laying a foundation for a future confirmatory RCT.

Study Design
The CUSA-1 trial is a monocenter randomized controlled patient and outcome assessor blinded pilot trial with two parallel study groups.

Study registration and ethics
The trial protocol was approved by the ethics committee of the University of Heidelberg (Ethikkommission Medizinische Fakultät Heidelberg, S-098/2022) and the trial was registered with the German clinical trial register (DRKS, DRKS00027474). All patient-related information is subject to medical confidentiality according to the European General Data Protection Regulation (Datenschutzgrundverordnung, DSGVO), the Federal Data Protection Act (Bundesdatenschutzgesetz) and the State Data Protection Act (Landesdatenschutzgesetz). Third parties will not have insight into original data. The trial will be performed according to the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

Patient and trial site
The trial will be conducted at the Clinical Trial Center (KSC) of the Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg. More than 150 distal pancreatectomies are performed each year at the Department of General, Visceral and Transplantation Surgery, which is certified as a center of excellence for pancreatic surgery by the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie). Thus, an estimated number of 10 patients will be screened per month and roughly half will be eligible for study inclusion. Therefore, the inclusion period is presumably 13-14 months. The duration of the overall trial is expected to be 24 months, including prearrangement and analysis. Randomization and data management are performed by the KSC.

Study population
All patients planned for elective open distal pancreatectomy for any indication are eligible for participation. Possible trial patients will be informed about the CUSA-1 trial, trial rationale, consequences and possible risks and benefits prior to their surgery either during their preoperative outpatient consultation or on the preoperative admission day. Participants may withdraw from the trial and stop their participation at any time on their own request without giving reasons for their decision.

Inclusion criteria:
- Patients planned for elective open distal pancreatectomy
- Patients age ≥ 18 years
- Ability to understand the character and individual consequences of the clinical trial
- Written informed consent

Exclusion criteria:
- Planned multivisceral resection, i.e. ≥ 3 organs, including arterial resections of the coeliac trunc and/or SMA (splenectomy, left adrenalectomy, and/or cholecystectomy are allowed and do

not count towards the definition of multivisceral resection, so are portal vein or SMV reconstructions)
- Minimally invasive surgical approach
- Lack of compliance or language difficulties that cause informed consent incomprehensible
- Participation in another intervention-trial with interference of intervention or outcome of this study
- Intraoperative: trial or control intervention not possible to perform due to decision of the operating surgeon (evaluated reasons will be assessed)

Surgical approach

Both groups
Midline or transverse incision may be performed according to surgeon's preference. A complete exploration of the abdomen will be done including frozen sections to define potentially curative resection. Entrance to the lesser sac is achieved by dissecting the omentum from the colon or by dissection of the gastrocolic ligament. After the resection phase the use of hemostyptics, sealants or autologous coverage such as teres ligament patch is not permitted. A haemostatic suture of the stapler-line is permitted as well as the application of somatostatin if considered necessary by the operating surgeon. All patients enrolled in this study are to receive a non-suction drainage before fascial closure. Abdominal wall closure, subcutaneous and skin closure methods are at the discretion of the operating surgeon and should be performed according to current standards.

Experimental intervention
When randomized to the experimental group, the dissection of the pancreas will be performed using the CUSA. All pancreatic ducts and side-branches along the transection plane that can be identified during dissection are to be selectively closed by either suture ligation or application of clips.

Control intervention
After mobilization of the portal vein plane either through an antegrade or retrograde approach, the dissection method is at the discretion of the operating surgeon and should be performed either with a surgical scalpel with subsequent suture closure of the pancreatic remnant or stapler dissection.

Outcome parameters
The development of grade B or C fistulas was chosen as primary endpoint to investigate the effect of the CUSA device on sealing of the pancreatic remnant and all its duct structures. A separated and pooled analyses (POPF Grade B, Grade C and Grade B and C) will be conducted. The assessment will be done according to the ISGPS consensus definitions[27] on visits 3-5 (Table 1) until postoperative day (POD) 30. Biochemical leaks (BL, formerly known as POPF A) will be assessed but do not count towards POPF as they do not require any deviation from the standard postoperative procedure. In patients not receiving a drainage (protocol violation), BL is eliminated as it cannot be assessed.
The primary safety endpoint will be postoperative complications according to Clavien-Dindo[28] grade ≥3, furthermore, the following secondary outcomes will be assessed separately until POD 30: chyle leak and PPH according to the ISGPS definition[29, 30], re-intervention, re-operation, re-hospitalization, intraabdominal fluid collection/ abscess, rate of burst abdomen, surgical site infection (SSI) according to the CDC-criteria[31], length of hospital stay, duration of intensive care unit (ICU) treatment, and mortality.

Randomization
Randomization will be performed intraoperatively after evaluation by the operating surgeon whether both, control or trial intervention, are equally possible and that intraoperative exclusion criteria such as necessary multivisceral resection or arterial reconstruction are not present. Randomization will be performed prior to pancreatic transection. Allocation of treatment will be performed using

sequentially numbered sealed envelopes generated by the responsible statistician by using block randomization with permuted block sizes. The randomization process and independently compiled assignment are performed by the KSC at the University Hospital Heidelberg. In the unlikely case, that after randomization, the control or trial intervention is not possible, e.g., due to unexpected inoperability, technical issues or the need for total pancreatectomy, the patient will be included in the intention to treat analysis.

Patient timelines and data collection

All patients with indication for open distal pancreatectomy will be screened consecutively for eligibility preoperatively. Patients fulfilling al inclusion but no exclusion criteria are enrolled into the study. Postoperative data collection is performed at the prespecified time points, and the regular visits will be performed by clinical investigators and study nurses from the clinical study center to collect information on the primary and secondary outcome parameters and to identify any postoperative complication (Table 1).

Blinding

Patients and outcome assessors will be blinded to the intervention to guarantee unbiased assessment of the endpoints as well as to reduce performance and detection bias. During the postoperative course randomized patients will neither be informed about group allocation nor the operative report and letter of discharge will contain any information hereof. Outcome assessors and data collectors will also be blinded to the trial intervention, the intraoperative randomization will be performed by an independent member of the KSC. As the operating surgeons cannot be blinded regarding the trial intervention, the clinical investigator is neither part of the surgical team nor has access to the randomization documents.

Safety aspects

Postoperative complications, recorded according to Clavien-Dindo classification, will be documented for evaluation of the primary safety endpoint. Complications with Clavien-Dindo grade ≥ 3 will be rated as “major complications”. All complications grade 4 and 5 will be blinded and reported to the coordinating investigator and to the steering committee, respectively, to detect any imbalance between both trial groups. Possible safety concerns that may arise for either technique will be evaluated, and a decision will be made whether an early termination of the trial seems necessary.

Sample size calculation

Based on the character of the CUSA-1 trial as a pilot study to gain first knowledge in this patient population, no formal sample size calculation was performed. After consultation with the statistics department and based on the annual operation numbers for distal pancreatectomies, we estimated that the recruitment of n=66 is feasible and reasonable in this pilot trial monocentric setting. Additionally, to date only one trial investigated CUSA in distal pancreatectomies in a randomized trial but in a different patient collective, therefore only limited data was available.

Due to the intraoperative randomization, expected low mortality and a short follow-up period (30 days), drop-outs after randomization are estimated to be low. Assuming a dropout rate of 10%, an inclusion of n=66 patients will result in n=60 patients to be analyzed in the final analysis. This sample size is sufficient to give first insights in the effect sizes of the considered endpoints in preparation for a subsequent confirmatory trial. The resulting maximal 95% confidence interval width for an effect size based on a binary endpoint is 47.6% (based on a control rate of 50%).

Statistical analysis

The statistical analysis of the primary and secondary endpoints will be based on the full analysis set built on the intention to treat principle, which means that all patients will be assessed in the group that they were randomized to.

The primary endpoint “development of a postoperative pancreatic fistula (POPF)” will be described by absolute and relative frequencies per study group. Rate difference will be reported as the effect size

together with the corresponding 95%-confidence interval. Boschloo's exact unconditional test will be performed to compare the rates between both study groups. In addition, analysis of the primary endpoint will be repeated in the as treated analysis set (AT). In the AT patients will be analyzed regarding to the intervention they actually received.
Regarding feasibility of the trial, recruitment rates and protocol violations will be considered and evaluated.
For analysis of the secondary endpoints, the empirical distribution of all endpoints will be calculated, including mean, standard deviation, and quartiles in case of continuous variables and scores, and with absolute and relative frequencies in case of categorical data. Whenever appropriate, statistical graphics will be used to visualize the findings. The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values. Missing data will be minimized by consequent documentation.
Due to the exploratory character of this study, p-values are only interpreted in a descriptive sense and no missing data will be imputed. However, drop-out cases will be considered carefully. In the analysis of safety endpoints, absolute and relative frequencies will be compared based on all randomized patients that underwent surgery in the group as treated. All analyses will be fully specified in a statistical analysis plan that is written prior to database closure. Analysis will be conducted in a validated R environment using R software, version 4.0.0 or higher.

Methods for minimizing bias

Minimizing selection bias
Randomization is the main countermeasure to tackle the issue of selection bias. Furthermore, all patients will be consecutively screened and if found to be eligible, informed consent will be obtained. Number of screened, included and analyzed patients will be reported and differences will be explained. Trial flow will be as depicted in figure 1.

Minimizing attrition bias
In this regard, on the one hand, all named endpoints are consistently recorded and reported, and on the other hand, an intention-to-treat analysis was chosen to reduce the impact of attrition bias. Follow-up was chosen as short as necessary and trial visits were reduced to a minimum to reduce further attrition.

Minimizing performance bias
To reduce performance bias all intra- and perioperative procedures will be the same in both groups (with exception of the resection phase) and will be performed to local standard operating procedures. To further minimize performance bias, all participating surgeons will be experienced in pancreatic surgery and will undergo a training regarding the use of the CUSA. Additionally, patient and assessor blinding further reduces performance bias.

Minimizing detection and reporting bias
This trial is registered with the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS00027474). To avoid the risk of selective reporting and to assure full transparency throughout the trial, the complete trial protocol will be published according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Supplemental Table 1) and subsequently all collected parameters named in this protocol will be published and analyzed in the final publication to avoid selective reporting[32, 33].
In order to reduce detection bias, outcome assessor blinding as well as standardized data collection during follow-up visits for both groups was implemented.

Patient involvement
The patient's perspective and needs were considered in various aspects in the development and implementation of this trial. The investigated research question - how to lower the occurrence of the

main postoperative complications after pancreatic surgery - was rated a *high priority* in a previously published interdisciplinary project "Priority Setting Partnership for Pancreatic Cancer" [34]. The project, equally involved all relevant stakeholders (including patients, relatives, caregivers and clinicians) in identifying the most important unanswered research questions in pancreatic cancer surgery. In addition, care was taken to keep the study visits as short and uncomplicated as possible in order to ensure a good feasibility and little effort for the patient.

Discussion

POPF is the most common and potentially dangerous complication following partial pancreatectomy with rates up to 30% after distal pancreatectomy.
A smooth postoperative course with an expeditious transition to ambulatory care is of great importance for a fast recovery and return to regular daily activities. Especially in pancreatic cancer surgery, POPF can lead to a serious delay or even termination of adjuvant therapeutic options, possibly rendering a desired multimodal tumor therapy insufficient. There is even evidence that an incomplete adjuvant chemotherapy after pancreatic cancer surgery has a negative impact on disease free survival[35]. While the delay or incompleteness of adjuvant therapies has an intermediate-term influence on patient's health, quality of life (QoL) and survival, the immediate and early postoperative severe complications arising from POPF may even be responsible for life-threatening circumstances within the 30-day postoperative period.

To enable a fast recovery, it needs to be highlighted that many perioperative influencing factors can be actively addressed to a certain extent, but especially some patient and organ associated factors still pose a challenge. The properties and texture of the pancreas itself represent an important example here. Especially a soft pancreas with small, hard to visualize, duct structures with the consequence of not entirely closed duct structures can increase the risk of clinically relevant POPF development[36, 37]. It is also known that intraoperative pancreatic leakage with discharge of enzyme rich fluid is a negative predictive factor as well[20, 38].
Currently, stapler transection or scalpel followed by suture closure are the standard methods for pancreas transection in distal pancreatectomy. In 2011, Diener et al. compared stapler versus conventional scalpel transection regarding the development of POPF in a multicenter RCT in distal pancreatectomy patients. The results showed that stapler was not superior to scalpel with similar POPF rates in both groups. Furthermore, a Cochrane meta-analysis performed in 2015 demonstrated a comparable rate of POPF of up to 35% for both closure methods[21].
With the CUSA device, a promising approach for pancreas transection has been previously reported but not yet confirmed in a homogenous patient population. To investigate the potential benefit of the device for open distal pancreatectomy, the CUSA-1 pilot trial will provide data in a randomized controlled setting regarding safety and the effect on POPF occurrence which will lay the foundation for a future confirmatory multicenter RCT.

Trial status

Recruitment of the CUSA-1 pilot trial started in April 2023 (first patient in on April 12th 2023). Recruitment is expected to be complete in 2024. The current version of the protocol is version 1.1, finalized on 2 June 2022.

Contributors

The study concept and design were conceived by FP and FH.
FP, ST, MF and RK assisted in refining the study questionnaires and study design. FP and MH are responsible for data collection. Statistics will be conducted by MF. MH and FP drafted the protocol manuscript and all authors critically revised the manuscript and approved the submitted version.

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Competing interests

None declared.

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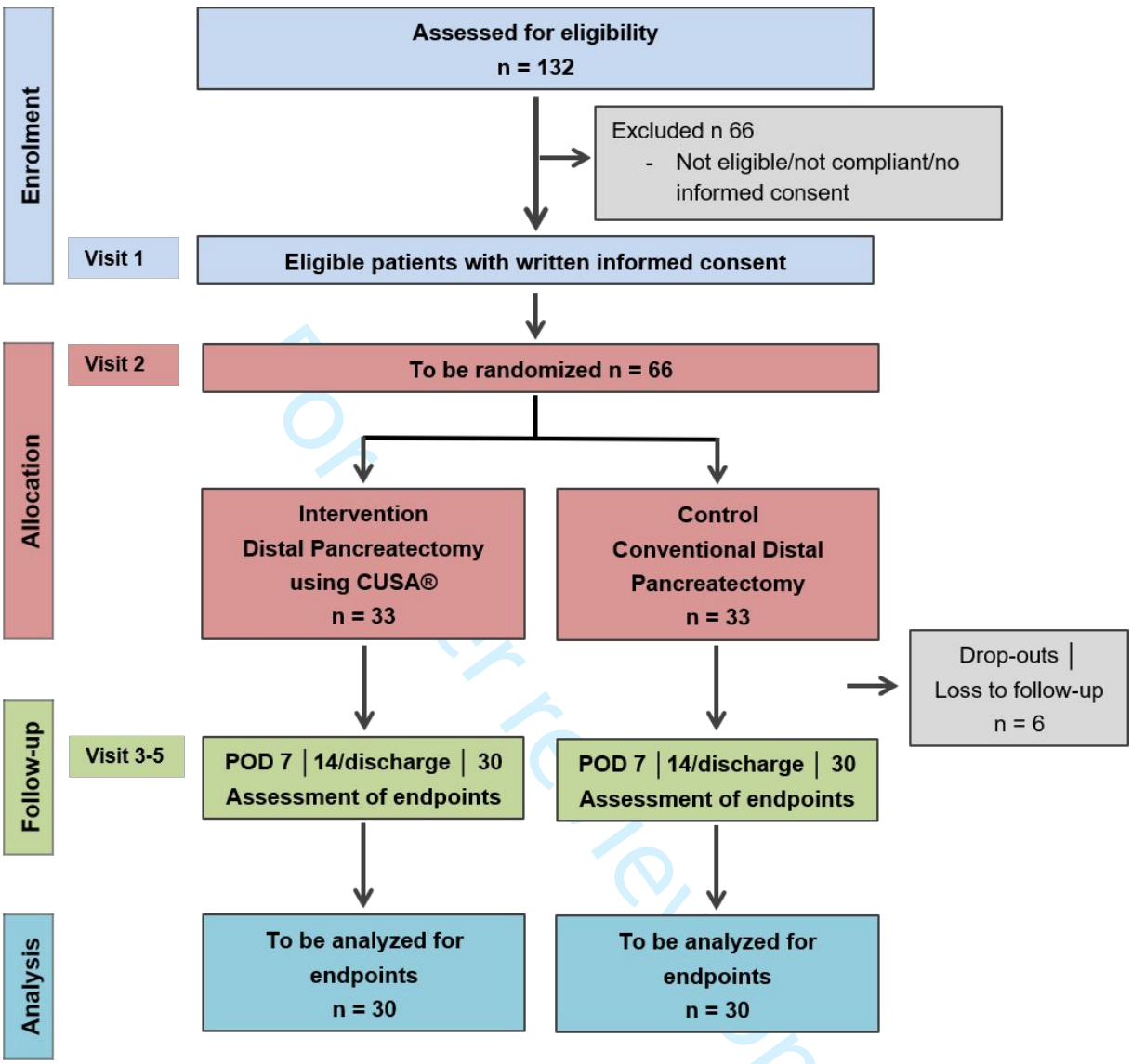
Figure 1: Trial flow chart of the CUSA-1 trial. POD: postoperative day



Supplementary Table 1. Reporting check list according to the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1, 8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 8
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4-5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4-5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation	5

		of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	4-5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4-5

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1, 3
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3-4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	3
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	1
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	-
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

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Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial

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Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial

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Abstract

Background:
Pancreatic fistula (POPF) remains the most common and serious complication after distal pancreatectomy. Many attempts at lowering fistula rates have led to unrewarding insignificant results as still up to 30% of the patients suffer from clinically relevant POPF. Therefore, the development of new innovative methods and procedures are still a cornerstone of current surgical research.
The CUSA device is a well-known ultrasound-based parenchyma transection method, often used in liver- and neurosurgery which has not yet been thoroughly investigated in pancreatic surgery, but first results seem very promising.

Methods:
The CUSA-1 trial is a randomized controlled pilot trial with two parallel study groups. This single-center trial is assessor and patient-blinded. A total of 60 patients with an indication for open distal pancreatectomy will be intraoperatively randomized after informed consent. The patients will be randomly assigned to either the control group with conventional pancreas transection (scalpel or stapler) or the experimental group, with transection using the CUSA device. The primary safety endpoint of this trial will be postoperative complications ≥ grade 3 according to the Clavien-Dindo classification. The primary endpoint to investigate the effect will be the rate of POPF within 30 days postoperatively according to the ISGPS definition. Further perioperative outcomes, including post-pancreatectomy hemorrhage (PPH), length of hospital stay and mortality will be analyzed as secondary endpoints.

Discussion:
Based on the available literature, CUSA may have a benefitable effect on POPF occurrence after distal pancreatectomy. The rationale of the CUSA-1 pilot trial is to investigate the safety and feasibility of the CUSA device in elective open distal pancreatectomy compared to conventional dissection methods and gather first data on the effect on POPF occurrence. This data will lay the groundwork for a future confirmatory multi-center randomized controlled trial.

Ethics and dissemination:
The CUSA-1 trial protocol was approved by the ethics committee of the University of Heidelberg (No. S-098/2022). Results will be published in an international peer-reviewed journal and summaries will be provided in lay language to study participants and their relatives.

Trial registration: German Clinical Trials Register (DRKS) DRKS00027474

Strengths and limitations of this study

- First study to assess safety and feasibility of the CUSA device in a pancreatic surgery patient population with prospectively structured assessment of data in a randomized controlled setting including blinding of patients and outcome assessors (reducing detection and performance bias)
- The presented trial will be designed and conducted according to all relevant regulations and guidelines resulting in a generally low risk of bias (according to the Cochrane Collaboration risk of bias tool)
- The trial provides valuable data allowing for planning and design of a future confirmatory multi-center trial
- The CUSA transection method is up until now only applicable in open distal pancreatectomy, limiting its use case
- The presented trial is a single-centre pilot trial, with lower internal and external validity

Background

Pancreatic surgery is a large and challenging field with approximately 10.000 annual partial pancreatectomies in Germany[1]. As the incidence of pancreatic cancer and therefore number of surgical interventions increases worldwide[2], the intra- and perioperative conditions have been continuously improved through further developments and standardization of processes[3-5]. The combination of increasing disease rates and thus complex pancreatic interventions with a considerable risk for complications still leads to a significant medical burden on the health care system[6, 7]. Postoperative pancreatic fistulas (POPF) are the most common and most serious complications after pancreatic surgery[8]. With an incidence varying from 10-15% for partial pancreatoduodenectomy and 20-30% for distal pancreatectomy according to the ISGPS-classification[9-12], the occurrence of POPF can decisively impair a patient's clinical course, as it may lead to further serious complications such as post-pancreatectomy hemorrhage (PPH), infections and even death in up to 33% in high risk populations[8, 13-15].

Many strategies and operative techniques have already been investigated with the aim of reducing POPF rates. A distinction regarding the different approaches can be made between remnant closure, pharmacological approaches, and the transection method itself. Several types of sealants for the pancreatic remnant after resection, such as fibrin glue or hemostyptics have been tested without desired results[16] Also, for mesh-augmentation no relevant efficacy could be measured[17]. The application of somatostatin analogues also failed to significantly reduce the rate of POPF development[18, 19]. The recently developed intraoperative pancreatic leakage indicator "SmartPAN", a device for the immediate detection of pancreatic leakages, is currently being investigated[20].

In addition to the above-mentioned methods, which mainly set after the transection process to seal the remaining pancreas, the third approach is to optimize the transection method itself. Up to date, the stapler or scalpel transection are the most common methods applied worldwide[15, 21]. However, the serious issue of POPF complication remains unsolved, and innovative methods for its prevention still need to be explored with high urgency.

In clinical routine, the CUSA device is frequently used in liver- and neurosurgery. It triggers tissue fragmentation depending on water concentration - tissue with higher water content (parenchyma) is fragmented faster than structures with a higher tissue content (vessels, duct structures). The tissue is then aspirated through the CUSA device exposing remaining duct and vessel structures, which can then be selectively ligated[22-24].

In as early as 1999, Suzuki et al. conducted a small RCT investigating the use of the Cavitron Ultrasonic Surgical Aspirator (CUSA, Integra lifesciences Corporation, NJ, USA) in comparison to conventional pancreas transection with scalpel in 27 (CUSA group) versus 31 (control group) patients undergoing distal pancreatectomy. The trial revealed a significantly lower POPF rate in the CUSA group (3.7% vs 25.8%, p=0.02)[25]. Despite these astonishing results, until now, no new RCTs were conducted on this approach. The rationale behind this finding might be the very precise tissue transection process when using the CUSA, so that even smallest pancreatic duct structures can be identified and sealed which possibly reduces the risk of POPF development. While CUSA was associated with a slightly longer transection time (23 vs 9 minutes), up to 30 tubular structures on the resection plane per patient were recognized including up to 6 pancreatic ducts each, which could then all be individually closed.

Unfortunately, in this trial, the patient population was very diverse and consisted of mainly locally advanced gastric cancer patients. In addition, only patients with non-fibrotic pancreatic parenchyma without main duct dilatation were included. Therefore, the internal and external study validity and especially transferability to patients with primary pancreatic lesions located in the body or tail are to some extent limited.

As the rationale and results of the above-mentioned trial are very promising and may have a substantial impact on the future of pancreatic surgery, it is our aim to investigate the CUSA method in an RCT in patients undergoing distal pancreatectomy for benign or malignant pancreatic pathologies. This will be the first pilot RCT with this patient population to investigate the CUSA transection technique with regard to POPF development.

Study design

Objective

The CUSA-1 trial investigates the safety and feasibility of the CUSA device in elective open distal pancreatectomy. This approach for pancreas transection will be compared with the conventional transection methods with scalpel or stapler. Data concerning safety and the effect on POPF occurrence as well as overall postoperative complications will be assessed. This study corresponds to a stage 2b investigation according to the IDEAL framework[26] and collects prospective data regarding safety and feasibility parameters in an exploratory character with the aim of laying a foundation for a future confirmatory RCT.

Study Design

The CUSA-1 trial is a monocenter randomized controlled patient and outcome assessor blinded pilot trial with two parallel study groups.

Study registration and ethics

The trial protocol was approved by the ethics committee of the University of Heidelberg (Ethikkommission Medizinische Fakultät Heidelberg, S-098/2022) and the trial was registered with the German clinical trial register (DRKS, DRKS00027474). All patient-related information is subject to medical confidentiality according to the European General Data Protection Regulation (Datenschutzgrundverordnung, DSGVO), the Federal Data Protection Act (Bundesdatenschutzgesetz) and the State Data Protection Act (Landesdatenschutzgesetz). Third parties will not have insight into original data. The trial will be performed according to the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

Patient and trial site

The trial will be conducted at the Clinical Trial Center (KSC) of the Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg. More than 150 distal pancreatectomies are performed each year at the Department of General, Visceral and Transplantation Surgery, which is certified as a center of excellence for pancreatic surgery by the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie). Thus, an estimated number of 10 patients will be screened per month and roughly half will be eligible for study inclusion. Therefore, the inclusion period is presumably 13-14 months. The duration of the overall trial is expected to be 24 months, including prearrangement and analysis. Randomization and data management are performed by the KSC.

Study population

All patients planned for elective open distal pancreatectomy for any indication are eligible for participation. Possible trial patients will be informed about the CUSA-1 trial, trial rationale, consequences and possible risks and benefits prior to their surgery either during their preoperative outpatient consultation or on the preoperative admission day. Participants may withdraw from the trial and stop their participation at any time on their own request without giving reasons for their decision.

Inclusion criteria:

- Patients planned for elective open distal pancreatectomy
- Patients age ≥ 18 years
- Ability to understand the character and individual consequences of the clinical trial
- Written informed consent

Exclusion criteria:

- Planned multivisceral resection, i.e. ≥ 3 organs, including arterial resections of the coeliac trunc and/or SMA (splenectomy, left adrenalectomy, and/or cholecystectomy are allowed and do not count towards the definition of multivisceral resection, so are portal vein or SMV reconstructions)
- Minimally invasive surgical approach
- Lack of compliance or language difficulties that cause informed consent incomprehensible
- Participation in another intervention-trial with interference of intervention or outcome of this study
- Intraoperative: trial or control intervention not possible to perform due to decision of the operating surgeon (evaluated reasons will be assessed)

Surgical approach

Both groups

Midline or transverse incision may be performed according to surgeon's preference. A complete exploration of the abdomen will be done including frozen sections to define potentially curative resection. Entrance to the lesser sac is achieved by dissecting the omentum from the colon or by dissection of the gastrocolic ligament. After the resection phase the use of hemostyptics, sealants or autologous coverage such as teres ligament patch is not permitted. A haemostatic suture of the stapler-line is permitted as well as the application of somatostatin if considered necessary by the operating surgeon. All patients enrolled in this study are to receive a non-suction drainage before fascial closure. Abdominal wall closure, subcutaneous and skin closure methods are at the discretion of the operating surgeon and should be performed according to current standards.

Experimental intervention

When randomized to the experimental group, the dissection of the pancreas will be performed using the CUSA. All pancreatic ducts and side-branches along the transection plane that can be identified during dissection are to be selectively closed by either suture ligation or application of clips.

Control intervention

After mobilization of the portal vein plane either through an antegrade or retrograde approach, the dissection method is at the discretion of the operating surgeon and should be performed either with a surgical scalpel with subsequent suture closure of the pancreatic remnant or stapler dissection.

Outcome parameters

The development of grade B or C fistulas was chosen as primary endpoint to investigate the effect of the CUSA device on sealing of the pancreatic remnant and all its duct structures. A separated and pooled analyses (POPF Grade B, Grade C and Grade B and C) will be conducted. The assessment will be done according to the ISGPS consensus definitions[27] on visits 3-5 (Table 1) until postoperative day (POD) 30. Biochemical leaks (BL, formerly known as POPF A) will be assessed but do not count towards POPF as they do not require any deviation from the standard postoperative procedure. In patients not receiving a drainage (protocol violation), BL is eliminated as it cannot be assessed.

The primary safety endpoint will be postoperative complications according to Clavien-Dindo[28] grade ≥3, furthermore, the following secondary outcomes will be assessed separately until POD 30: chyle leak and PPH according to the ISGPS definition[29, 30], re-intervention, re-operation, re-hospitalization, intraabdominal fluid collection/ abscess, rate of burst abdomen, surgical site infection (SSI) according to the CDC-criteria[31], length of hospital stay, duration of intensive care unit (ICU) treatment, and mortality.

To assess feasibility of the CUSA device, recruitment rate, intraoperative reasons for drop-outs and number and severity of protocol violations will be documented.

Table 1: Trial visits and documented parameters

Visit	**1** Screening	**2** Surgery	**3** POD 7±2	**4** POD 14±2/ discharge	**5** POD 30±2 (phone interview)
Inclusion					
Informed consent	**X**				
Eligibility criteria	**X**				
Randomization/Allocation		**X**			
Surgical intervention		**X**			
Assessments					
- Demographics and baseline clinical data	**X**				
- Assessment of surgical data		**X**			
- Assessment of clinical endpoints			**X**	**X**	**X**

POD: postoperative day

Randomization

Randomization will be performed intraoperatively after evaluation by the operating surgeon whether both, control or trial intervention, are equally possible and that intraoperative exclusion criteria such as necessary multivisceral resection or arterial reconstruction are not present. Randomization will be performed prior to pancreatic transection. Allocation of treatment will be performed using sequentially numbered sealed envelopes generated by the responsible statistician by using block randomization with permuted block sizes. The randomization process and independently compiled assignment are performed by the KSC at the University Hospital Heidelberg. In the unlikely case, that after randomization, the control or trial intervention is not possible, e.g., due to unexpected inoperability, technical issues or the need for total pancreatectomy, the patient will be included in the intention to treat analysis.

Patient timelines and data collection

All patients with indication for open distal pancreatectomy will be screened consecutively for eligibility preoperatively. Patients fulfilling al inclusion but no exclusion criteria are enrolled into the study. Postoperative data collection is performed at the prespecified time points, and the regular visits will be performed by clinical investigators and study nurses from the clinical study center to collect information on the primary and secondary outcome parameters and to identify any postoperative complication (Table 1).

Blinding

Patients and outcome assessors will be blinded to the intervention to guarantee unbiased assessment of the endpoints as well as to reduce performance and detection bias. During the postoperative course randomized patients will neither be informed about group allocation nor the operative report and letter of discharge will contain any information hereof. Outcome assessors and data collectors will also be blinded to the trial intervention, the intraoperative randomization will be performed by an independent member of the KSC. As the operating surgeons cannot be blinded regarding the trial intervention, the clinical investigator is neither part of the surgical team nor has access to the randomization documents.

Safety aspects

Postoperative complications, recorded according to Clavien-Dindo classification, will be documented for evaluation of the primary safety endpoint. Complications with Clavien-Dindo grade ≥ 3 will be rated as “major complications”. All complications grade 4 and 5 will be blinded and reported to the coordinating investigator and to the steering committee, respectively, to detect any imbalance

between both trial groups. Possible safety concerns that may arise for either technique will be evaluated, and a decision will be made whether an early termination of the trial seems necessary.

Sample size calculation

Based on the character of the CUSA-1 trial as a pilot study to gain first knowledge in this patient population, no formal sample size calculation was performed. After consultation with the statistics department and based on the annual operation numbers for distal pancreatectomies, we estimated that the recruitment of n=66 is feasible and reasonable in this pilot trial monocentric setting. Additionally, to date only one trial investigated CUSA in distal pancreatectomies in a randomized trial but in a different patient collective, therefore only limited data was available.

Due to the intraoperative randomization, expected low mortality and a short follow-up period (30 days), drop-outs after randomization are estimated to be low. Assuming a dropout rate of 10%, an inclusion of n=66 patients will result in n=60 patients to be analyzed in the final analysis. This sample size is sufficient to give first insights in the effect sizes of the considered endpoints in preparation for a subsequent confirmatory trial. The resulting maximal 95% confidence interval width for an effect size based on a binary endpoint is 47.6% (based on a control rate of 50%).

Statistical analysis

The statistical analysis of the primary and secondary endpoints will be based on the full analysis set built on the intention to treat principle, which means that all patients will be assessed in the group that they were randomized to.

The primary endpoint “development of a postoperative pancreatic fistula (POPF)” will be described by absolute and relative frequencies per study group. Rate difference will be reported as the effect size together with the corresponding 95%-confidence interval. Boschloo’s exact unconditional test will be performed to compare the rates between both study groups. In addition, analysis of the primary endpoint will be repeated in the as treated analysis set (AT). In the AT patients will be analyzed regarding to the intervention they actually received.

Regarding feasibility of the trial, recruitment rates and protocol violations will be considered and evaluated.

For analysis of the secondary endpoints, the empirical distribution of all endpoints will be calculated, including mean, standard deviation, and quartiles in case of continuous variables and scores, and with absolute and relative frequencies in case of categorical data. Whenever appropriate, statistical graphics will be used to visualize the findings. The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values. Missing data will be minimized by consequent documentation.

Due to the exploratory character of this study, p-values are only interpreted in a descriptive sense and no missing data will be imputed. However, drop-out cases will be considered carefully. In the analysis of safety endpoints, absolute and relative frequencies will be compared based on all randomized patients that underwent surgery in the group as treated. All analyses will be fully specified in a statistical analysis plan that is written prior to database closure. Analysis will be conducted in a validated R environment using R software, version 4.0.0 or higher.

Methods for minimizing bias

Minimizing selection bias

Randomization is the main countermeasure to tackle the issue of selection bias. Furthermore, all patients will be consecutively screened and if found to be eligible, informed consent will be obtained. Number of screened, included and analyzed patients will be reported and differences will be explained. Trial flow will be as depicted in figure 1.

Minimizing attrition bias

In this regard, on the one hand, all named endpoints are consistently recorded and reported, and on the other hand, an intention-to-treat analysis was chosen to reduce the impact of attrition bias. Follow-

up was chosen as short as necessary and trial visits were reduced to a minimum to reduce further attrition.

Minimizing performance bias

To reduce performance bias all intra- and perioperative procedures will be the same in both groups (with exception of the resection phase) and will be performed to local standard operating procedures. To further minimize performance bias, all participating surgeons will be experienced in pancreatic surgery and will undergo a training regarding the use of the CUSA. Additionally, patient and assessor blinding further reduces performance bias.

Minimizing detection and reporting bias

This trial is registered with the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS00027474). To avoid the risk of selective reporting and to assure full transparency throughout the trial, the complete trial protocol will be published according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Supplemental Table 1) and subsequently all collected parameters named in this protocol will be published and analyzed in the final publication to avoid selective reporting[32, 33].

In order to reduce detection bias, outcome assessor blinding as well as standardized data collection during follow-up visits for both groups was implemented.

Patient involvement

The patient's perspective and needs were considered in various aspects in the development and implementation of this trial. The investigated research question - how to lower the occurrence of the main postoperative complications after pancreatic surgery - was rated a *high priority* in a previously published interdisciplinary project "Priority Setting Partnership for Pancreatic Cancer" [34]. The project, equally involved all relevant stakeholders (including patients, relatives, caregivers and clinicians) in identifying the most important unanswered research questions in pancreatic cancer surgery. In addition, care was taken to keep the study visits as short and uncomplicated as possible in order to ensure a good feasibility and little effort for the patient.

Discussion

POPF is the most common and potentially dangerous complication following partial pancreatectomy with rates up to 30% after distal pancreatectomy.
A smooth postoperative course with an expeditious transition to ambulatory care is of great importance for a fast recovery and return to regular daily activities. Especially in pancreatic cancer surgery, POPF can lead to a serious delay or even termination of adjuvant therapeutic options, possibly rendering a desired multimodal tumor therapy insufficient. There is even evidence that an incomplete adjuvant chemotherapy after pancreatic cancer surgery has a negative impact on disease free survival[35]. While the delay or incompleteness of adjuvant therapies has an intermediate-term influence on patient's health, quality of life (QoL) and survival, the immediate and early postoperative severe complications arising from POPF may even be responsible for life-threatening circumstances within the 30-day postoperative period.

To enable a fast recovery, it needs to be highlighted that many perioperative influencing factors can be actively addressed to a certain extent, but especially some patient and organ associated factors still pose a challenge. The properties and texture of the pancreas itself represent an important example here. Especially a soft pancreas with small, hard to visualize, duct structures with the consequence of not entirely closed duct structures can increase the risk of clinically relevant POPF development[36, 37]. It is also known that intraoperative pancreatic leakage with discharge of enzyme rich fluid is a negative predictive factor as well[20, 38].
Currently, stapler transection or scalpel followed by suture closure are the standard methods for pancreas transection in distal pancreatectomy. In 2011, Diener et al. compared stapler versus conventional scalpel transection regarding the development of POPF in a multicenter RCT in distal pancreatectomy patients. The results showed that stapler was not superior to scalpel with similar POPF rates in both groups. Furthermore, a Cochrane meta-analysis performed in 2015 demonstrated a comparable rate of POPF of up to 35% for both closure methods[21].
With the CUSA device, a promising approach for pancreas transection has been previously reported but not yet confirmed in a homogenous patient population. To investigate the potential benefit of the device for open distal pancreatectomy, the CUSA-1 pilot trial will provide data in a randomized controlled setting regarding safety and the effect on POPF occurrence which will lay the foundation for a future confirmatory multicenter RCT.

Trial status

Recruitment of the CUSA-1 pilot trial started in April 2023 (first patient in on April 12th 2023). Recruitment is expected to be complete in 2024. The current version of the protocol is version 1.1, finalized on 2 June 2022.

Contributors

The study concept and design were conceived by FP and FH.
FP, ST, MF and RK assisted in refining the study questionnaires and study design. FP and MH are responsible for data collection. Statistics will be conducted by MF. MH and FP drafted the protocol manuscript and all authors critically revised the manuscript and approved the submitted version.

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Competing interests

None declared.

Figure legends

Figure 1. Trial flow chart of the CUSA-1 trial. POD: postoperative day

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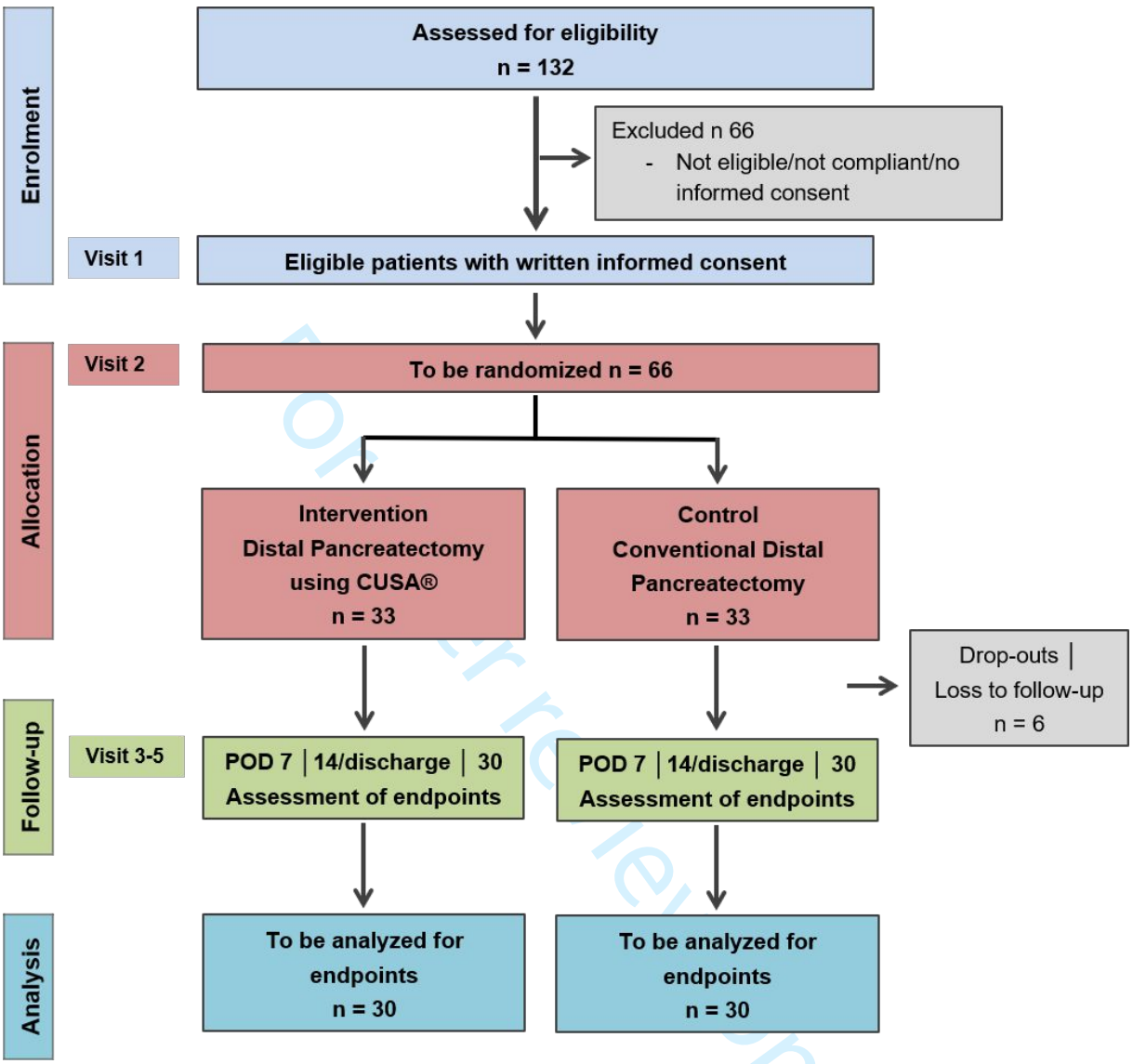
Figure 1: Trial flow chart of the CUSA-1 trial. POD: postoperative day



Supplementary Table 1. Reporting check list according to the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1, 8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 8
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4-5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4-5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation	5

		of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	4-5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4-5

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1, 3
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3-4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	3
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	1
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	-
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

BMJ Open

Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial

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Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial

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Abstract

Background:
Pancreatic fistula (POPF) remains the most common and serious complication after distal pancreatectomy. Many attempts at lowering fistula rates have led to unrewarding insignificant results as still up to 30% of the patients suffer from clinically relevant POPF. Therefore, the development of new innovative methods and procedures are still a cornerstone of current surgical research.
The CUSA device is a well-known ultrasound-based parenchyma transection method, often used in liver- and neurosurgery which has not yet been thoroughly investigated in pancreatic surgery, but first results seem very promising.

Methods:
The CUSA-1 trial is a randomized controlled pilot trial with two parallel study groups. This single-center trial is assessor and patient-blinded. A total of 60 patients with an indication for open distal pancreatectomy will be intraoperatively randomized after informed consent. The patients will be randomly assigned to either the control group with conventional pancreas transection (scalpel or stapler) or the experimental group, with transection using the CUSA device. The primary safety endpoint of this trial will be postoperative complications ≥ grade 3 according to the Clavien-Dindo classification. The primary endpoint to investigate the effect will be the rate of POPF within 30 days postoperatively according to the ISGPS definition. Further perioperative outcomes, including post-pancreatectomy hemorrhage (PPH), length of hospital stay and mortality will be analyzed as secondary endpoints.

Discussion:
Based on the available literature, CUSA may have a benefitable effect on POPF occurrence after distal pancreatectomy. The rationale of the CUSA-1 pilot trial is to investigate the safety and feasibility of the CUSA device in elective open distal pancreatectomy compared to conventional dissection methods and gather first data on the effect on POPF occurrence. This data will lay the groundwork for a future confirmatory multi-center randomized controlled trial.

Ethics and dissemination:
The CUSA-1 trial protocol was approved by the ethics committee of the University of Heidelberg (No. S-098/2022). Results will be published in an international peer-reviewed journal and summaries will be provided in lay language to study participants and their relatives.

Trial registration: German Clinical Trials Register (DRKS) DRKS00027474

Strengths and limitations of this study

- First single center randomized controlled pilot trial comparing the CUSA device with conventional dissection methods in distal pancreatectomy patients regarding the occurrence of pancreatic fistula
- The trial design is conducted according to all relevant regulations and guidelines resulting in a generally low risk of bias (according to the Cochrane Collaboration risk of bias tool)
- The trial provides valuable data on safety and feasibility allowing for planning and design of a future confirmatory multi-center trial
- The CUSA transection method is up until now only applicable in open distal pancreatectomy, limiting its use case
- The presented trial is a single-center pilot trial, with lower internal and external validity

Background

Pancreatic surgery is a large and challenging field with approximately 10.000 annual partial pancreatectomies in Germany[1]. As the incidence of pancreatic cancer and therefore number of surgical interventions increases worldwide[2], the intra- and perioperative conditions have been continuously improved through further developments and standardization of processes[3-5]. The combination of increasing disease rates and thus complex pancreatic interventions with a considerable risk for complications still leads to a significant medical burden on the health care system[6, 7]. Postoperative pancreatic fistulas (POPF) are the most common and most serious complications after pancreatic surgery[8]. With an incidence varying from 10-15% for partial pancreatoduodenectomy and 20-30% for distal pancreatectomy according to the ISGPS-classification[9-12], the occurrence of POPF can decisively impair a patient's clinical course, as it may lead to further serious complications such as post-pancreatectomy hemorrhage (PPH), infections and even death in up to 33% in high risk populations[8, 13-15].

Many strategies and operative techniques have already been investigated with the aim of reducing POPF rates. A distinction regarding the different approaches can be made between remnant closure, pharmacological approaches, and the transection method itself. Several types of sealants for the pancreatic remnant after resection, such as fibrin glue or hemostyptics have been tested without desired results[16] Also, for mesh-augmentation no relevant efficacy could be measured[17]. The application of somatostatin analogues also failed to significantly reduce the rate of POPF development[18, 19]. The recently developed intraoperative pancreatic leakage indicator "SmartPAN", a device for the immediate detection of pancreatic leakages, is currently being investigated[20].

In addition to the above-mentioned methods, which mainly set after the transection process to seal the remaining pancreas, the third approach is to optimize the transection method itself. Up to date, the stapler or scalpel transection are the most common methods applied worldwide[15, 21]. However, the serious issue of POPF complication remains unsolved, and innovative methods for its prevention still need to be explored with high urgency.

In clinical routine, the CUSA device is frequently used in liver- and neurosurgery. It triggers tissue fragmentation depending on water concentration - tissue with higher water content (parenchyma) is fragmented faster than structures with a higher tissue content (vessels, duct structures). The tissue is then aspirated through the CUSA device exposing remaining duct and vessel structures, which can then be selectively ligated[22-24].

In as early as 1999, Suzuki et al. conducted a small RCT investigating the use of the Cavitron Ultrasonic Surgical Aspirator (CUSA, Integra lifesciences Corporation, NJ, USA) in comparison to conventional pancreas transection with scalpel in 27 (CUSA group) versus 31 (control group) patients undergoing distal pancreatectomy. The trial revealed a significantly lower POPF rate in the CUSA group (3.7% vs 25.8%, p=0.02)[25]. Despite these astonishing results, until now, no new RCTs were conducted on this approach. The rationale behind this finding might be the very precise tissue transection process when using the CUSA, so that even smallest pancreatic duct structures can be identified and sealed which possibly reduces the risk of POPF development. While CUSA was associated with a slightly longer transection time (23 vs 9 minutes), up to 30 tubular structures on the resection plane per patient were recognized including up to 6 pancreatic ducts each, which could then all be individually closed.

Unfortunately, in this trial, the patient population was very diverse and consisted of mainly locally advanced gastric cancer patients. In addition, only patients with non-fibrotic pancreatic parenchyma without main duct dilatation were included. Therefore, the internal and external study validity and especially transferability to patients with primary pancreatic lesions located in the body or tail are to some extent limited.

As the rationale and results of the above-mentioned trial are very promising and may have a substantial impact on the future of pancreatic surgery, it is our aim to investigate the CUSA method in an RCT in patients undergoing distal pancreatectomy for benign or malignant pancreatic pathologies. This will be the first pilot RCT with this patient population to investigate the CUSA transection technique with regard to POPF development.

Study design

Objective
The CUSA-1 trial investigates the safety and feasibility of the CUSA device in elective open distal pancreatectomy. This approach for pancreas transection will be compared with the conventional transection methods with scalpel or stapler. Data concerning safety and the effect on POPF occurrence as well as overall postoperative complications will be assessed. This study corresponds to a stage 2b investigation according to the IDEAL framework[26] and collects prospective data regarding safety and feasibility parameters in an exploratory character with the aim of laying a foundation for a future confirmatory RCT.

Study Design
The CUSA-1 trial is a monocenter randomized controlled patient and outcome assessor blinded pilot trial with two parallel study groups.

Study registration and ethics
The trial protocol was approved by the ethics committee of the University of Heidelberg (Ethikkommission Medizinische Fakultät Heidelberg, S-098/2022) and the trial was registered with the German clinical trial register (DRKS, DRKS00027474). All patient-related information is subject to medical confidentiality according to the European General Data Protection Regulation (Datenschutzgrundverordnung, DSGVO), the Federal Data Protection Act (Bundesdatenschutzgesetz) and the State Data Protection Act (Landesdatenschutzgesetz). Third parties will not have insight into original data. The trial will be performed according to the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki.

Patient and trial site
The trial will be conducted at the Clinical Trial Center (KSC) of the Department of General, Visceral and Transplantation Surgery, University Hospital Heidelberg. More than 150 distal pancreatectomies are performed each year at the Department of General, Visceral and Transplantation Surgery, which is certified as a center of excellence for pancreatic surgery by the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie). Thus, an estimated number of 10 patients will be screened per month and roughly half will be eligible for study inclusion. Therefore, the inclusion period is presumably 13-14 months. The duration of the overall trial is expected to be 24 months, including prearrangement and analysis. Randomization and data management are performed by the KSC.

Study population
All patients planned for elective open distal pancreatectomy for any indication are eligible for participation. Possible trial patients will be informed about the CUSA-1 trial, trial rationale, consequences and possible risks and benefits prior to their surgery either during their preoperative outpatient consultation or on the preoperative admission day. Participants may withdraw from the trial and stop their participation at any time on their own request without giving reasons for their decision.

Inclusion criteria:
- Patients planned for elective open distal pancreatectomy
- Patients age ≥ 18 years
- Ability to understand the character and individual consequences of the clinical trial
- Written informed consent

Exclusion criteria:
- Planned multivisceral resection, i.e. ≥ 3 organs, including arterial resections of the coeliac trunc and/or SMA (splenectomy, left adrenalectomy, and/or cholecystectomy are allowed and do

not count towards the definition of multivisceral resection, so are portal vein or SMV reconstructions)
- Minimally invasive surgical approach
- Lack of compliance or language difficulties that cause informed consent incomprehensible
- Participation in another intervention-trial with interference of intervention or outcome of this study
- Intraoperative: trial or control intervention not possible to perform due to decision of the operating surgeon (evaluated reasons will be assessed)

Surgical approach

Both groups

Midline or transverse incision may be performed according to surgeon's preference. A complete exploration of the abdomen will be done including frozen sections to define potentially curative resection. Entrance to the lesser sac is achieved by dissecting the omentum from the colon or by dissection of the gastrocolic ligament. After the resection phase the use of hemostyptics, sealants or autologous coverage such as teres ligament patch is not permitted. A haemostatic suture of the stapler-line is permitted as well as the application of somatostatin if considered necessary by the operating surgeon. All patients enrolled in this study are to receive a non-suction drainage before fascial closure. Abdominal wall closure, subcutaneous and skin closure methods are at the discretion of the operating surgeon and should be performed according to current standards.

Experimental intervention

When randomized to the experimental group, the dissection of the pancreas will be performed using the CUSA. All pancreatic ducts and side-branches along the transection plane that can be identified during dissection are to be selectively closed by either suture ligation or application of clips.

Control intervention

After mobilization of the portal vein plane either through an antegrade or retrograde approach, the dissection method is at the discretion of the operating surgeon and should be performed either with a surgical scalpel with subsequent suture closure of the pancreatic remnant or stapler dissection.

Outcome parameters

The development of grade B or C fistulas was chosen as primary endpoint to investigate the effect of the CUSA device on sealing of the pancreatic remnant and all its duct structures. A separated and pooled analyses (POPF Grade B, Grade C and Grade B and C) will be conducted. The assessment will be done according to the ISGPS consensus definitions[27] on visits 3-5 (Table 1) until postoperative day (POD) 30. Biochemical leaks (BL, formerly known as POPF A) will be assessed but do not count towards POPF as they do not require any deviation from the standard postoperative procedure. In patients not receiving a drainage (protocol violation), BL is eliminated as it cannot be assessed.

The primary safety endpoint will be postoperative complications according to Clavien-Dindo[28] grade ≥3, furthermore, the following secondary outcomes will be assessed separately until POD 30: chyle leak and PPH according to the ISGPS definition[29, 30], re-intervention, re-operation, re-hospitalization, intraabdominal fluid collection/ abscess, rate of burst abdomen, surgical site infection (SSI) according to the CDC-criteria[31], length of hospital stay, duration of intensive care unit (ICU) treatment, and mortality.

To assess feasibility of the CUSA device, recruitment rate, intraoperative reasons for drop-outs and number and severity of protocol violations will be documented.

Table 1: Trial visits and documented parameters

Visit	1 Screening	2 Surgery	3 POD 7±2	4 POD 14±2/ discharge	5 POD 30±2 (phone interview)
Inclusion					
Informed consent	**X**				
Eligibility criteria	**X**				
Randomization/Allocation		**X**			
Surgical intervention		**X**			
Assessments					
- Demographics and baseline clinical data	**X**				
- Assessment of surgical data		**X**			
- Assessment of clinical endpoints			**X**	**X**	**X**

POD: postoperative day

Randomization

Randomization will be performed intraoperatively after evaluation by the operating surgeon whether both, control or trial intervention, are equally possible and that intraoperative exclusion criteria such as necessary multivisceral resection or arterial reconstruction are not present. Randomization will be performed prior to pancreatic transection. Allocation of treatment will be performed using sequentially numbered sealed envelopes generated by the responsible statistician by using block randomization with permuted block sizes. The randomization process and independently compiled assignment are performed by the KSC at the University Hospital Heidelberg. In the unlikely case, that after randomization, the control or trial intervention is not possible, e.g., due to unexpected inoperability, technical issues or the need for total pancreatectomy, the patient will be included in the intention to treat analysis.

Patient timelines and data collection

All patients with indication for open distal pancreatectomy will be screened consecutively for eligibility preoperatively. Patients fulfilling al inclusion but no exclusion criteria are enrolled into the study. Postoperative data collection is performed at the prespecified time points, and the regular visits will be performed by clinical investigators and study nurses from the clinical study center to collect information on the primary and secondary outcome parameters and to identify any postoperative complication (Table 1).

Blinding

Patients and outcome assessors will be blinded to the intervention to guarantee unbiased assessment of the endpoints as well as to reduce performance and detection bias. During the postoperative course randomized patients will neither be informed about group allocation nor the operative report and letter of discharge will contain any information hereof. Outcome assessors and data collectors will also be blinded to the trial intervention, the intraoperative randomization will be performed by an independent member of the KSC. As the operating surgeons cannot be blinded regarding the trial intervention, the clinical investigator is neither part of the surgical team nor has access to the randomization documents.

Safety aspects

Postoperative complications, recorded according to Clavien-Dindo classification, will be documented for evaluation of the primary safety endpoint. Complications with Clavien-Dindo grade ≥ 3 will be rated as “major complications”. All complications grade 4 and 5 will be blinded and reported to the coordinating investigator and to the steering committee, respectively, to detect any imbalance between both trial groups. Possible safety concerns that may arise for either technique will be evaluated, and a decision will be made whether an early termination of the trial seems necessary.

Sample size calculation

Based on the character of the CUSA-1 trial as a pilot study to gain first knowledge in this patient population, no formal sample size calculation was performed. After consultation with the statistics department and based on the annual operation numbers for distal pancreatectomies, we estimated that the recruitment of n=66 is feasible and reasonable in this pilot trial monocentric setting. Additionally, to date only one trial investigated CUSA in distal pancreatectomies in a randomized trial but in a different patient collective, therefore only limited data was available.

Due to the intraoperative randomization, expected low mortality and a short follow-up period (30 days), drop-outs after randomization are estimated to be low. Assuming a dropout rate of 10%, an inclusion of n=66 patients will result in n=60 patients to be analyzed in the final analysis. This sample size is sufficient to give first insights in the effect sizes of the considered endpoints in preparation for a subsequent confirmatory trial. The resulting maximal 95% confidence interval width for an effect size based on a binary endpoint is 47.6% (based on a control rate of 50%).

Statistical analysis

The statistical analysis of the primary and secondary endpoints will be based on the full analysis set built on the intention to treat principle, which means that all patients will be assessed in the group that they were randomized to.

The primary endpoint “development of a postoperative pancreatic fistula (POPF)” will be described by absolute and relative frequencies per study group. Rate difference will be reported as the effect size together with the corresponding 95%-confidence interval. Boschloo’s exact unconditional test will be performed to compare the rates between both study groups. In addition, analysis of the primary endpoint will be repeated in the as treated analysis set (AT). In the AT patients will be analyzed regarding to the intervention they actually received.

Regarding feasibility of the trial, recruitment rates and protocol violations will be considered and evaluated.

For analysis of the secondary endpoints, the empirical distribution of all endpoints will be calculated, including mean, standard deviation, and quartiles in case of continuous variables and scores, and with absolute and relative frequencies in case of categorical data. Whenever appropriate, statistical graphics will be used to visualize the findings. The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values. Missing data will be minimized by consequent documentation.

Due to the exploratory character of this study, p-values are only interpreted in a descriptive sense and no missing data will be imputed. However, drop-out cases will be considered carefully. In the analysis of safety endpoints, absolute and relative frequencies will be compared based on all randomized patients that underwent surgery in the group as treated. All analyses will be fully specified in a statistical analysis plan that is written prior to database closure. Analysis will be conducted in a validated R environment using R software, version 4.0.0 or higher.

Methods for minimizing bias

Minimizing selection bias

Randomization is the main countermeasure to tackle the issue of selection bias. Furthermore, all patients will be consecutively screened and if found to be eligible, informed consent will be obtained. Number of screened, included and analyzed patients will be reported and differences will be explained. Trial flow will be as depicted in figure 1.

Minimizing attrition bias

In this regard, on the one hand, all named endpoints are consistently recorded and reported, and on the other hand, an intention-to-treat analysis was chosen to reduce the impact of attrition bias. Follow-up was chosen as short as necessary and trial visits were reduced to a minimum to reduce further attrition.

Minimizing performance bias

To reduce performance bias all intra- and perioperative procedures will be the same in both groups (with exception of the resection phase) and will be performed to local standard operating procedures. To further minimize performance bias, all participating surgeons will be experienced in pancreatic surgery and will undergo a training regarding the use of the CUSA. Additionally, patient and assessor blinding further reduces performance bias.

Minimizing detection and reporting bias

This trial is registered with the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS00027474). To avoid the risk of selective reporting and to assure full transparency throughout the trial, the complete trial protocol will be published according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Supplemental Table 1) and subsequently all collected parameters named in this protocol will be published and analyzed in the final publication to avoid selective reporting[32, 33].

In order to reduce detection bias, outcome assessor blinding as well as standardized data collection during follow-up visits for both groups was implemented.

Patient involvement

The patient's perspective and needs were considered in various aspects in the development and implementation of this trial. The investigated research question - how to lower the occurrence of the main postoperative complications after pancreatic surgery - was rated a *high priority* in a previously published interdisciplinary project "Priority Setting Partnership for Pancreatic Cancer" [34]. The project, equally involved all relevant stakeholders (including patients, relatives, caregivers and clinicians) in identifying the most important unanswered research questions in pancreatic cancer surgery. In addition, care was taken to keep the study visits as short and uncomplicated as possible in order to ensure a good feasibility and little effort for the patient.

Discussion

POPF is the most common and potentially dangerous complication following partial pancreatectomy with rates up to 30% after distal pancreatectomy.
A smooth postoperative course with an expeditious transition to ambulatory care is of great importance for a fast recovery and return to regular daily activities. Especially in pancreatic cancer surgery, POPF can lead to a serious delay or even termination of adjuvant therapeutic options, possibly rendering a desired multimodal tumor therapy insufficient. There is even evidence that an incomplete adjuvant chemotherapy after pancreatic cancer surgery has a negative impact on disease free survival[35]. While the delay or incompleteness of adjuvant therapies has an intermediate-term influence on patient's health, quality of life (QoL) and survival, the immediate and early postoperative severe complications arising from POPF may even be responsible for life-threatening circumstances within the 30-day postoperative period.

To enable a fast recovery, it needs to be highlighted that many perioperative influencing factors can be actively addressed to a certain extent, but especially some patient and organ associated factors still pose a challenge. The properties and texture of the pancreas itself represent an important example here. Especially a soft pancreas with small, hard to visualize, duct structures with the consequence of not entirely closed duct structures can increase the risk of clinically relevant POPF development[36, 37]. It is also known that intraoperative pancreatic leakage with discharge of enzyme rich fluid is a negative predictive factor as well[20, 38].
Currently, stapler transection or scalpel followed by suture closure are the standard methods for pancreas transection in distal pancreatectomy. In 2011, Diener et al. compared stapler versus conventional scalpel transection regarding the development of POPF in a multicenter RCT in distal pancreatectomy patients. The results showed that stapler was not superior to scalpel with similar POPF rates in both groups. Furthermore, a Cochrane meta-analysis performed in 2015 demonstrated a comparable rate of POPF of up to 35% for both closure methods[21].
With the CUSA device, a promising approach for pancreas transection has been previously reported but not yet confirmed in a homogenous patient population. To investigate the potential benefit of the device for open distal pancreatectomy, the CUSA-1 pilot trial will provide data in a randomized controlled setting regarding safety and the effect on POPF occurrence which will lay the foundation for a future confirmatory multicenter RCT.

Trial status

Recruitment of the CUSA-1 pilot trial started in April 2023 (first patient in on April 12th 2023). Recruitment is expected to be complete in 2024. The current version of the protocol is version 1.1, finalized on 2 June 2022.

Contributors

The study concept and design were conceived by FP and FH.
FP, ST, MF and RK assisted in refining the study questionnaires and study design. FP and MH are responsible for data collection. Statistics will be conducted by MF. MH and FP drafted the protocol manuscript and all authors critically revised the manuscript and approved the submitted version.

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Competing interests

None declared.

Figure legends

Figure 1. Trial flow chart of the CUSA-1 trial. POD: postoperative day

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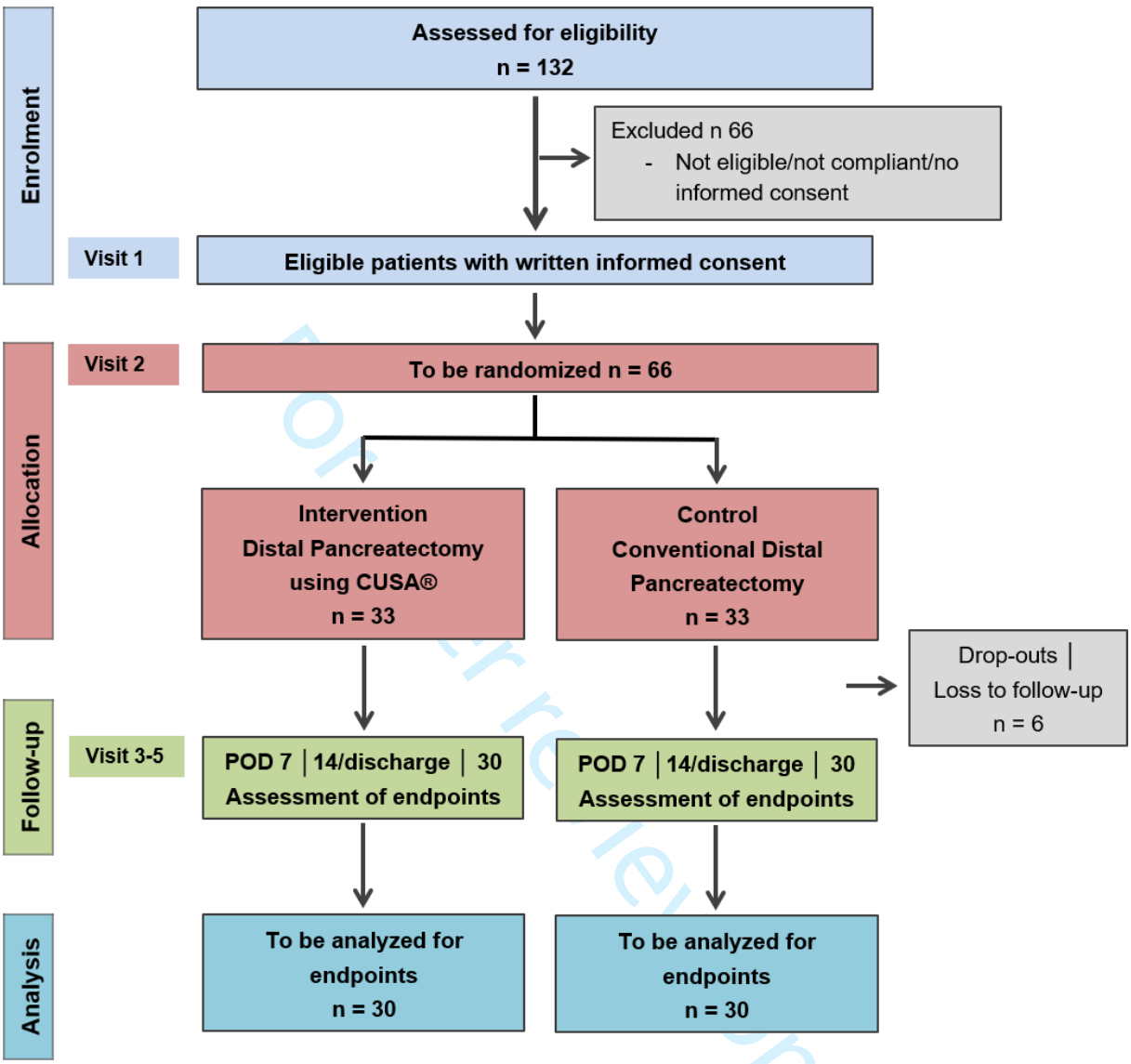
Figure 1: Trial flow chart of the CUSA-1 trial. POD: postoperative day



Supplementary Table 1. Reporting check list according to the SPIRIT guidelines.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	8
Funding	#4	Sources and types of financial, material, and other support	8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	8
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1, 8
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1, 8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1, 8
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	2-3
Objectives	#7	Specific objectives or hypotheses	2-3
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	4-5
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	4-5
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-5
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation	5

		of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	4-5
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4-5

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	1, 3
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	-
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3-4
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	3
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	1
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	1
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	-
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-