

BMJ Open Cavitron ultrasonic surgical aspirator (CUSA) compared with conventional pancreatic transection in distal pancreatectomy: study protocol for the randomised controlled CUSA-1 pilot trial

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To cite: Holze M, Loos M, Hüttner F, *et al.* Cavitron ultrasonic surgical aspirator (CUSA) compared with conventional pancreatic transection in distal pancreatectomy: study protocol for the randomised controlled CUSA-1 pilot trial. *BMJ Open* 2024;**14**:e082024. doi:10.1136/bmjopen-2023-082024

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2023-082024>).

Received 12 November 2023
Accepted 08 March 2024



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ABSTRACT

Background Postoperative 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 is still a cornerstone of current surgical research.

The cavitron ultrasonic surgical aspirator (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 the first results seem very promising.

Methods The CUSA-1 trial is a randomised controlled pilot trial with two parallel study groups. This single-centre trial is assessor and patient blinded. A total of 60 patients with an indication for open distal pancreatectomy will be intraoperatively randomised 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 $\geq$ 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 postpancreatectomy haemorrhage, length of hospital stay and mortality will be analysed as secondary endpoints.

Discussion Based on the available literature, CUSA may have a beneficial 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 with conventional dissection methods and gather the first data on the effect on POPF occurrence. This data will lay the groundwork for a future confirmatory multicentre randomised controlled trial.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ First single-centre randomised controlled pilot trial comparing the cavitron ultrasonic surgical aspirator (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 multicentre trial.
- ⇒ The CUSA transection method is well-established mainly in open surgery and therefore will be only used in open distal pancreatectomy during the trial.
- ⇒ The presented trial is a single-centre pilot trial, with limited internal and external validity.

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 number DRKS00027474.

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, the number of surgical interventions increases worldwide,² the intraoperative and perioperative conditions have been continuously improved through further developments and standardisation 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 healthcare system.^{6,7} Postoperative pancreatic fistulas (POPFs) are the most common and most serious complications after pancreatic surgery.⁸ With an incidence varying from 10% to 15% for partial pancreateoduodenectomy and from 20% to 30% for distal pancreatectomy according to the international study group on pancreatic surgery (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 postpancreatectomy haemorrhage (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 haemostyptics 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 are mainly set after the transection process to seal the remaining pancreas, the third approach is to optimise the transection method itself. Up to date, the stapler or scalpel transection is 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 cavitron ultrasonic surgical aspirator (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}

As early as 1999, Suzuki *et al* conducted a small RCT investigating the use of the CUSA (Integra lifesciences Corporation, New Jersey, USA) in comparison to conventional pancreas transection with scalpel in 27 (CUSA group) vs 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 randomised controlled trials (RCTs) have been conducted on this approach. The rationale behind this finding might be the very precise tissue transection process when using the CUSA, so that even the 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 min), up to 30 tubular structures on the resection plane per patient were recognised 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 framework²⁶ 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 monocentre randomised 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), the Federal Data Protection Act (Bundesdatenschutzgesetz) and the State Data Protection Act (Landesdatenschutzgesetz). Third parties will not have insight into the original data. The trial will be performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Patient and trial site

The trial will be conducted at the Clinical Trial Centre ("Klinisches Studienzentrum Chirurgie", 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 centre 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 prearrangements and analysis. Randomisation 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, that is, ≥ 3 organs, including arterial resections of the coeliac trunk 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 haemostyptics, 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 randomised 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 mobilisation 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 analysis (POPF grade B, grade C and grades B and C) will be conducted. The assessment will be done according to the ISGPS consensus definitions²⁷ 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-Dindo²⁸ 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} reintervention, reoperation, rehospitalisation, intra-abdominal fluid collection/ abscess, rate of burst abdomen, surgical site infection according to the CDC criteria,³¹ length of hospital stay, duration of intensive care unit treatment and mortality.

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

Randomisation

Randomisation will be performed intraoperatively after evaluation by the operating surgeon whether both,

Table 1 Trial visits and documented parameters

Visit	1	2	3	4	5
	Screening	Surgery	POD 7±2	POD 14±2/ discharge	POD 30±2 (phone interview)
Inclusion					
Informed consent	X				
Eligibility criteria	X				
Randomisation/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.

control or trial intervention, are equally possible and that intraoperative exclusion criteria such as necessary multivisceral resection or arterial reconstruction are not present. Randomisation 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 randomisation with permuted block sizes. The randomisation process and independently compiled assignment are performed by the KSC at the University Hospital Heidelberg. In the unlikely case, that after randomisation, the control or trial intervention is not possible, for example, 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 all 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 centre 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, randomised 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 randomisation 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 randomisation 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 grades 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 of 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 randomised trial but in a different patient collective, therefore, only limited data were available.

Due to the intraoperative randomisation, expected low mortality and a short follow-up period (30 days), drop-outs after randomisation are estimated to be low. Assuming a drop-out rate of 10%, an inclusion of $n=66$ patients will result in $n=60$ patients to be analysed in the final analysis. This sample size is sufficient to give first insights into the effect sizes of the considered endpoints in preparation for a subsequent confirmatory trial. The resulting maximal 95% CI 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 randomised to.

The primary endpoint ‘development of a 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% CI. 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 analysed regarding 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, SD 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 visualise 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 minimised 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 randomised 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, V.4.0.0 or higher.

Methods for minimising bias

Minimising selection bias

Randomisation 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 analysed patients will be reported and differences will be explained. Trial flow will be as depicted in figure 1.

Minimising 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

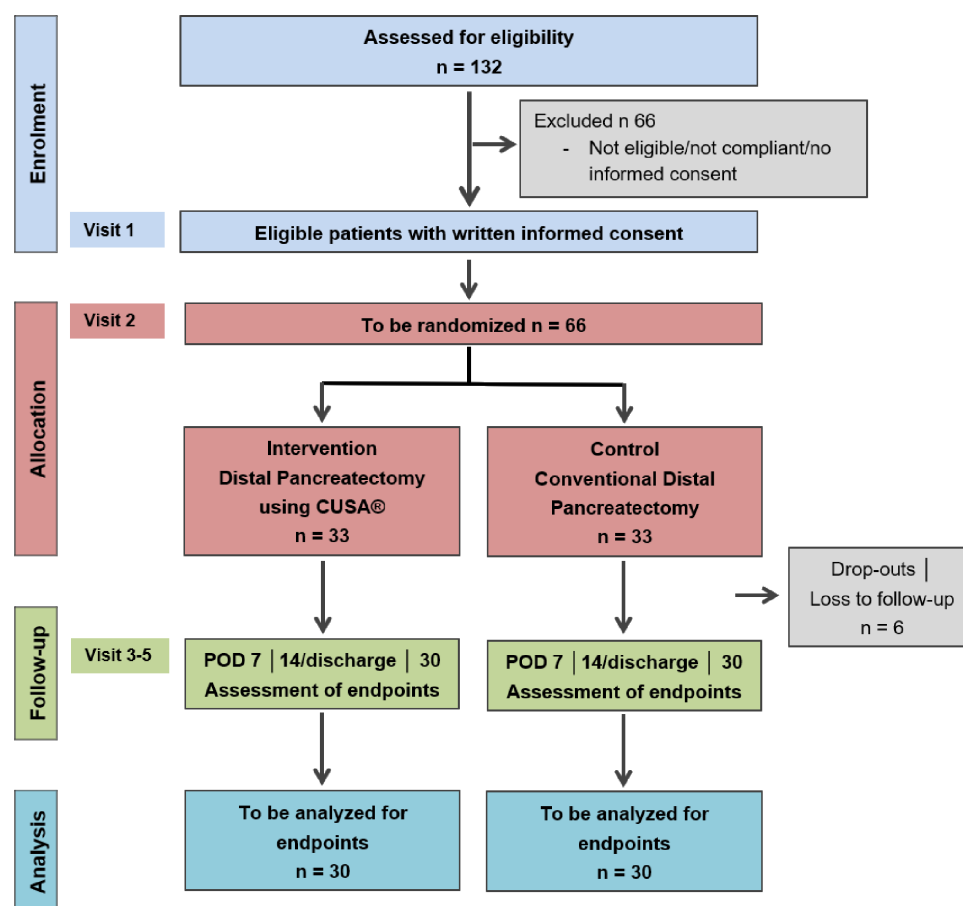


Figure 1 Trial flow chart of the CUSA-1 trial. CUSA, cavitron ultrasonic surgical aspirator; POD, postoperative day.

as necessary and trial visits were reduced to a minimum to reduce further attrition.

Minimising performance bias

To reduce performance bias, all intraoperative and perioperative procedures will be the same in both groups (with exception of the resection phase) and will be performed according to local standard operating procedures. To further minimise 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.

Minimising 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 statement (online supplemental table 1) and subsequently all collected parameters named in this protocol will be published and analysed in the final publication to avoid selective reporting.^{32 33}

In order to reduce detection bias, outcome assessor blinding as well as standardised 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 tumour 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 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 visualise, 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. Diener *et al* compared stapler versus conventional scalpel transection regarding the development of POPF in a multicentre 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 homogeneous patient population. To investigate the potential benefit of the device for open distal pancreatectomy, the CUSA-1 pilot trial will provide data in a randomised controlled setting regarding safety and the effect on POPF occurrence which will lay the foundation for a future confirmatory multicentre RCT.

TRIAL STATUS

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

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Contributors FP, FH, MH, PK, MF and RK developed the trial concept and wrote the protocol and the manuscript of the protocol publication. ML, CM, AM and ST helped to develop the trial concept and revised the manuscript critically for important intellectual content. All authors approved the final version for publication agreed to

be accountable for all aspects of the work and ensure that any questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

Funding This study is financially supported by the Heidelberger Stiftung Chirurgie (grant number 2021/467).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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