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Intraoperative visualisation of pancreatic leakage (ViP): study protocol for an IDEAL Stage I Post Market Clinical Study

Thomas M Pausch ,[1] Magdalena Holze,[1,2] Bodil Gesslein,[3] Inga Rossion,[2] Franziska von Eisenhart Rothe,[1] Martin Wagner,[1,2] Anja Sander,[4] Solveig Tenckhoff,[2] Marc Bartel,[5] Jan Larmann ,[6] Pascal Probst ,[1,7] Frank Pianka,[1] Thilo Hackert,[1] Rosa Klotz[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Thomas M Pausch;
thomas.pausch@med.uni-heidelberg.de

ABSTRACT

Introduction Pancreatic resections are an important field of surgery worldwide to treat a variety of benign and malignant diseases. Postoperative pancreatic fistula (POPF) remains a frequent and critical complication after partial pancreatectomy and affects up to 50% of patients. POPF increases mortality, prolongs the postoperative hospital stay and is associated with a significant economic burden. Despite various scientific approaches and clinical strategies, it has not yet been possible to develop an effective preventive tool. The SmartPAN indicator is the first surgery-ready medical device for direct visualisation of pancreatic leakage already during the operation. Applied to the surface of pancreatic tissue, it detects sites of biochemical leak via colour reaction, thereby guiding effective closure and potentially mitigating POPF development.

Methods and analysis The ViP trial is a prospective single-arm, single-centre first in human study to collect data on usability and confirm safety of SmartPAN. A total of 35 patients with planned partial pancreatectomy will be included in the trial with a follow-up of 30 days after the index surgery. Usability endpoints such as adherence to protocol and evaluation by the operating surgeon as well as safety parameters including major intraoperative and postoperative complications, especially POPF development, will be analysed.

Ethics and dissemination Following the IDEAL-D (Idea, Development, Exploration, Assessment, and Long term study of Device development and surgical innovation) framework of medical device development preclinical in vitro, porcine in vivo, and human ex vivo studies have proven feasibility, efficacy and safety of SmartPAN. After market approval, the ViP trial is the IDEAL Stage I trial to investigate SmartPAN in a clinical setting. The study has been approved by the local ethics committee as the device is used exclusively within its intended purpose. Results will be published in a peer-reviewed journal. The study will provide a basis for a future randomised controlled interventional trial to confirm clinical efficacy of SmartPAN.

Trial registration number German Clinical Trial Register DRKS00027559, registered on 4 March 2022.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ SmartPAN medical device development has been fully conducted in accordance with IDEAL-D framework and after preclinical proof of feasibility, efficacy and safety the Visualisation of pancreatic leakage trial represents a derisked translation to clinical stage (stage I).
⇒ By design, trial participants receive unaltered state-of-the art pancreatic surgery plus additional intraoperative indication of pancreatic biochemical leakage and potentially effective targeted leak closure.
⇒ Limitation of the trial is its single-arm single-centre exploratory design with focus on usability and safety that will require a subsequent randomised controlled trial to confirm SmartPAN's clinical efficacy.

INTRODUCTION

Context

Pancreatic surgery is the only curative therapeutic approach in many benign and especially malignant pathologies. Despite the fact, that advanced surgical techniques, perioperative care improvements and centralisation in specialised high-volume centres have led to mortality rates of under 5%,[1–4] pancreatic surgery is still complex with a considerable risk for complications and an overall morbidity of more than 50%.[3 5 6] One of the most frequent and critical complications after partial pancreatectomy is postoperative pancreatic fistula (POPF).[7] A leakage of enzyme-rich pancreatic fluid either from the pancreatic remnant, for example after distal pancreatectomy or pancreatic enucleation, or from the pancreatic anastomosis, for example after partial pancreatoduodenectomy, can lead to severe consequences such as sepsis or postpancreatectomy haemorrhage.[8] POPF affects up to 50% of patients following pancreatic surgery and is associated

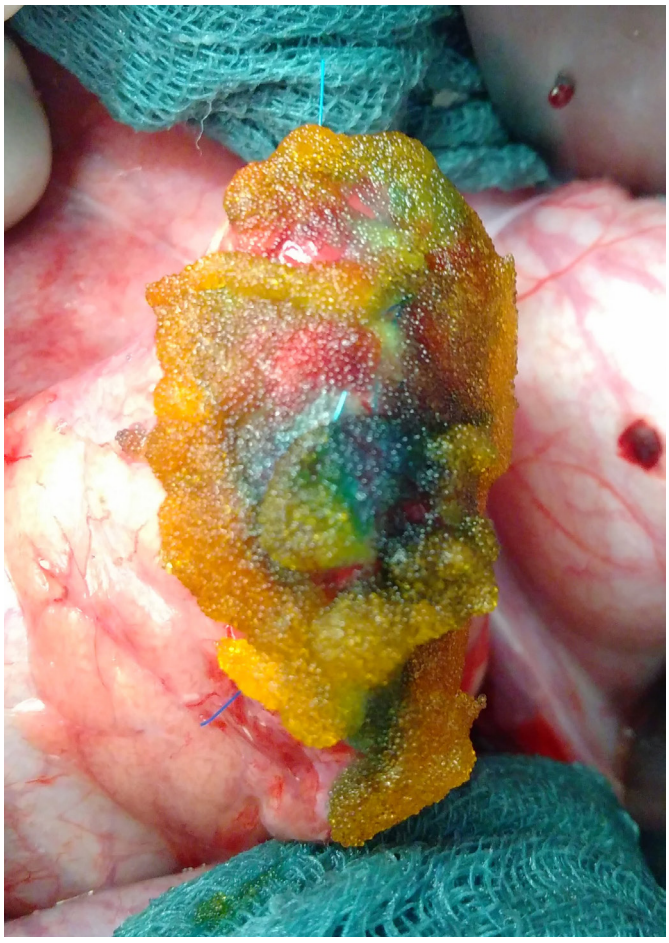

Figure 1 Representative image of SmartPAN blue colour reaction to leakage at the pancreatic remnant after distal pancreatectomy in porcine animal trial. Photo credit: TMP.

with a prolonged hospital stay and a significant economic burden.[5 9–12] Furthermore, in-hospital mortality due to POPF or subsequent complications reaches up to 33% in high-risk subgroups.[2 9]

Current knowledge

Many attempts have been made to reduce the POPF occurrence such as development of different techniques for pancreatic dissection,[13] application of drugs like somatostatin analogues[14] or intraoperative usage of sealants such as fibrin glue or haemostyptics[15] without ground-breaking success. An auspicious chance would be to detect the leakage of pancreatic fluid during surgery, as high concentrations of pancreatic enzymes in intraoperatively derived abdominal fluid are highly predictive for POPF.[16] An intraoperative indicator visualising leakage could enable immediate targeted closure of the detected leakage sites, optimised drain placement and postoperative care and thus lead to a reduction of clinically relevant POPF. However, since pancreatic fluid is physiologically invisible no suitable tool has been developed before to identify leakage sites in routine clinical use.[17–21] Recently, a novel indicator for pancreatic leakage called SmartPAN has been developed according to the IDEAL-D framework for surgical innovation and medical devices.[22–24] SmartPAN contains the pH-indicator bromothymol blue (BTB) bound to an active biodegradable polysaccharide-microsphere matrix to detect alkali pancreatic fluid and phosphate buffered saline. It is applied to the pancreatic surface in the surgical area in one continuous layer. Appearing orange when applied, it locally turns green bluish over pancreatic leakage (figure 1). During development, one superior indicator for pancreatic fluid was selected for further evaluation.[25] This prototype was assessed in vivo using a porcine model (Sus scrofa domesticus) for usability, effectiveness and reliability. Treatment groups were defined by SmartPAN-reaction at initial pancreatic resection: indicator positive or negative. Indicator-positive individuals randomly received either targeted closure of leakage sites or no further closure. SmartPAN's reliability and effectiveness were assessed by monitoring abdominal drainage for pancreatic enzymes and with relaparotomy after 48 hours. SmartPAN responses were consistent between both surgical procedures and conformed to amylase measurements. In a consecutive preclinical randomised efficacy trial, SmartPAN was capable of precisely detecting sites associated with biochemical leak and subsequent clinical POPF-symptoms with high sensitivity and specificity, thereby guiding effective closure.[26] Preclinical safety assessments did not show cytotoxicity at concentrations used in practise.[27] It was shown that SmartPAN consists of components that are either biocompatible or quickly neutralised by dilution and drainage. Therefore, the preclinical IDEAL stage 0 has been completed[28] with proof of efficacy and safety providing a derisked translation to first-in-human studies.

METHODS AND ANALYSIS

Objective

According to the IDEAL-D framework the visualisation of pancreatic leakage (ViP) trial represents a stage I first in human trial.[22–24] Hence, this post-market clinical follow-up (PMCF) trial aims to confirm the usability and safety of the indicator application in the clinical environment of elective pancreatic resections when used according to the instructions for use. Usability, safety and previously unknown side-effects or contraindications of the indicator in the clinical environment of elective pancreatic resection will be assessed.

Trial design

ViP is a prospective investigator-initiated single-arm single-centre study.

Patient and public involvement

Establishing SmartPAN in clinical routine could be a big step towards the best complication treatment after pancreatic surgery, a goal which we have shown to be a research priority of utmost relevance identified by patients, caregivers and professional stakeholders in our

priority setting partnership project[29] (also see Ethics and dissemination section). Trial results will be discussed with the patient advisory board of the SDGC for interpretation and for preparation of subsequent trials.

Study population

The study will be conducted at the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital. Annually, more than 700 pancreatic surgeries are conducted at this high-volume centre. Enrolment of patients was started on 27 June 2022 and completion of the trial is expected in February 2023. Accounting for interfering trials, conservatively 5 patients per month are expected to be included and completion of recruitment is feasible within 7 months. All patients with planned partial pancreatectomy will be screened consecutively for eligibility. They will be informed about the ViP-trial during a pretreatment visit or on the day of hospitalisation. Eligible for participation are (1) all patients with diseases of the pancreas which necessitate partial pancreatectomy with open or minimally invasive surgical approach. Additionally, (2) age≥18 years and (3) the capability to understand the subject and individual consequences of the clinical trial have been chosen as inclusion criteria. Exclusion criteria are defined as follows: (1) American Society of Anesthesiologists (ASA) Score>3, (2) pregnancy or lactation, (3) known allergy or intolerability to BTB or potato starch, (4) participation in another intervention trial with interference of intervention and outcome of this study, (5) any condition which could result in an undue risk for the patient in the opinion of the clinical investigator, (6) expected lack of compliance or language problems. Patients may withdraw from the trial at their own request at any time without giving reasons. If no partial pancreatic resection is performed (e.g., because of technical irresectability or metastatic disease) or if the investigator stops the trial intervention due to expected harm to the patient's well-being, the respective patient will leave the trial early (see Sample size calculation section). This will be detailed in the final report of the trial to ensure complete transparency.

Intervention

All participating surgeons will be experienced in pancreatic surgery. To ensure recognition of experience as well as device usage, a self-categorisation will be performed by the surgeons (online supplemental file 1). Surgeons will be trained regarding study-specific handling instructions for the investigational device by the principal investigator prior to the study initiation. Laparoscopic or open partial pancreatectomy is performed according to local standard operating procedures. In case of distal pancreatectomy, a stapler will be used for closure of the remnant pancreas and no additional covering (e.g., teres ligament patch) will be conducted. In case of partial pancreatoduodenectomy, reconstruction includes a pancreaticojejunostomy, a hepaticojejunostomy and a duodenojejunostomy or gastrojejunostomy. Somatostatin or analogues will not be given postoperatively as a matter of routine. However, if applied usage must be documented and justified. After accomplished resection and reconstruction phase and haemostasis, the SmartPAN indicator is applied in a standardised procedure as specified in the instructions for use of the device: prior to application, the operative field is gently rinsed and dabbed to ensure complete blood dryness which could possibly reduce effectiveness of the indicator. The target area is maintained in a horizontal position and approximately 4 mL of the indicator hydrogel is applied rapidly and uniformly to the cut surface/pancreatic anastomosis, taking care to cover the whole tissue of interest and to prevent overspill. Depending on the surgeon's preference, application can be performed solely with the original syringe or with additional surgical standard application devices. The surrounding area will be covered with sterile surgical gauzes to guarantee contact of the indicator only to the tissue of interest. Colour change only appears close to relevant pancreatic leakage (figure 1). The observation time for any colour change is defined as up to 3 min after application. In case of subsequent localised colour change, extra single stiches may be applied to close pancreatic leakage depending on the operating surgeon's preference and SmartPAN may be reapplied to confirm closure tightness. Nature of colour change (speed of appearance, number and size of spots, optical discrimination, durability) and subsequent targeted closure will be reported (online supplemental file 1). After usage, the surgical site is rinsed with sterile isotone saline and drainage or suctioning of the fluid is assured to avoid accumulation of the product in the abdominal cavity.

To investigate concentration of BTB in patients, venous blood samples will be taken from central venous catheter 15 min after indicator application. This timepoint takes into account the maximum intra-abdominal BTB concentration known from preclinical studies at approximately 5 min plus a latency for potential systemic absorption. According to standard surgical procedure, a drainage is inserted into abdominal cavity or drainage omission is documented if not inserted. Easy-flow drainages in case of open surgery and Robinson drainages in case of minimally invasive surgery are placed next to the remnant of the pancreas before the abdominal wall is closed. A sample from the intraperitoneal drain fluid will be taken for the assessment of BTB and amylase/lipase concentrations at the end of surgery. At the second postoperative day, drain fluid is checked for amylase/lipase and BTB. If enzyme concentrations are <3 times institutional normal serum values, the drain is typically removed on day 2 or 3. If values are high, the drain is kept longer, and enzyme concentrations will be rechecked until drain removal according to standard clinical procedure.

Outcome parameters

The chosen endpoints cover important usability endpoints as well as safety endpoints represented by clinical intraoperative and postoperative parameters including

Table 1 Definition of outcome parameters

Endpoint	*Definition*
Usability endpoints	
Adherence to study protocol including SmartPAN instructions for use	Recording of all deviations from the study protocol with justification.
Usability evaluation of SmartPAN by operating surgeon	Surgeon's usability score with six dimensions (experience, ease of use, usefulness, ease of learning, intention to use, safety; see online supplemental file 1).
Safety and efficacy endpoints	
Major intraoperative and postoperative complication and relation to SmartPAN usage	Complications classified according to Clavien-Dindo[30] grade III-V within 30 days after the index surgery including information on potential relation to usage of SmartPAN.
Duration of surgery (min)	Time from the beginning of skin incision to the end of skin closure.
Intraoperative blood loss (mL)	Volume of blood loss as recorded in the anesthesiology report.
Postoperative pancreatic fistula (%)	Rate of postoperative biochemical leak and grade B and C POPF within 30 days after the index surgery as defined by the ISGPS.[7]
Non-surgical reinterventions	Occurrence of non-surgical reinterventions within 30 days after the index operation (eg, image-guided drain placement, angiography with stenting/ other interventions, endoscopy).
Reoperations	Occurrence of reoperations within 30 days after the index surgery.
Mortality (%)	Rate of deaths within 30 days after the index surgery.
Health-related quality of life (HRQoL)	Differences in health-related quality of life measured by the SF-36 at baseline and at the 30th day after the index surgery.[31]
Concentration of bromothymol blue (degradation product of SmartPAN) in central venous blood and in abdominal fluid (ng/mL)	Measured in central venous blood 15 min after SmartPAN application and at the second day after the index surgery. Measured in abdominal drainage fluid at the end of surgery and at the second day after the index surgery.

patient-reported outcome and laboratory outcomes. For a detailed list of all measured outcome parameters, see table 1.

Participant timeline

Patients will undergo follow-up within 30 days after the index surgery. Preoperative and postoperative data collection will be performed at six visits which will be conducted by clinical investigators and study nurses as mentioned in table 2. During the screening visit (visit 1, 1–7 days prior surgery), patients will be included in the trial if they fulfil all inclusion criteria and do not meet any exclusion criteria. Baseline demographic and clinical data will be collected during visit 1. Intraoperative data will be recorded during visit 2 including the indicator usability score (online supplemental file 1), collection of one central venous blood sample and of one drain fluid

Table 2 Trial visits

	1	2	3	4	5	6
	Screening	Day of surgery	POD 2	POD 7	Day of discharge	POD 30
Visit	Outpatient/ inpatient	Inpatient				Outpatient/ telephone
Eligibility criteria	X					
Informed consent	X					
Baseline demographics and clinical data	X					
Surgical intervention		X				
Assessment of usability		X				
Assessment of safety		X	X	X	X	X
Assessment of efficacy		X	X	X	X	X

POD, postoperative day

sample. During the follow-up visits 3–5 on postoperative day 2, 7 and the day of discharge safety and efficacy data items and information about their potential relation to use the trial device are documented, like the occurrence of POPF[7] or other major postoperative complications (classified as Clavien-Dindo grade III to V[30]), non-surgical reinterventions or reoperations. Additionally, at visit 3 on postoperative day 2, central venous blood and abdominal drain fluid will be examined for BTB concentration and for amylase and lipase. Visit 6 will take place as a telephone interview at postoperative day 30 and includes a survey of health-related quality of life measured by the SF-36 questionnaire.[31]

Safety aspects

All Clavien-Dindo grade III–V complications will undergo further assessment and the potential relationship to the use of the trial device will be investigated. If immediate action is required concerning the continuation of the trial, the principal investigator and the steering committee will be informed and will decide if any modifications or precautions regarding the trial procedure are needed. Serious incidents will be reported to the device manufacturer Magle Chemoswed AB Holding (Malmö, Sweden) within 24 hours. These include Clavien-Dindo grade III–V events that are considered to be medical device related. Device malfunction incidents and other serious events such as the death of a patient or other person, the temporary or permanent serious deterioration of a patient's, user's or other person's state of health or a serious public health threat will be reported as well.

Sample size calculation

Due to the fact that this is an exploratory trial, no formal sample size calculation was performed. Analysis of 30 patients was judged sufficient for a preliminary evaluation of usability and safety of the SmartPAN device. Considering that approximately 5 patients will be excluded due to inoperability or the implementation of another type of pancreatectomy, an overall number of 35 patients will be allocated to the trial (figure 2). From previous randomised controlled trials on distal pancreatectomy and partial pancreatectomy and from a review of the literature, there is good evidence that the rate of POPF after distal pancreatectomy is 40%[6 13] and 20% after partial pancreatoduodenectomy.[5 32] Accordingly, we expect about 10 patients to develop a POPF and SmartPAN-driven closure attempts by the operating surgeon will be described and compared with literature controls as basis for subsequent interventional trials.

Statistical analysis

Endpoints are described as mean values along with SD, median values, and quartiles, minimum and maximum for continuous, and relative and absolute frequencies for categorical endpoints. Regarding the use of SmartPAN, adherence and usability will be analysed qualitatively and quantitatively in the whole study group and in the subgroups of the two most common types of surgery, respectively. The safety analysis includes calculation of frequencies and rates of major complications (Clavien-Dindo grade III–V) together with 95% CI. Statistical analyses will be fully specified in a statistical analysis plan that is written prior to database closure. All analyses will be exploratory, having only descriptive character and will be done using SAS (SAS Institute) V.9.4 or higher.

Data collection and data management

Study data will be collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Study Center of the German Society of Surgery at Heidelberg University Hospital. REDCap is a secure, web-based software platform designed to support data capture for research studies.[33 34] An electronic case report form (eCRF) will be used for data collection. All information collected during the trial will be entered in the eCRF by the study investigators or study nurses. The eCRF pages will be completed as soon as possible, preferably on the same day that a trial participant is undergoing trial procedure step. Any outstanding entries will be completed immediately after the final visit. An explanation should be given for all missing data. To assure a safe and secure environment for acquired data, transmission is encrypted with secure socket layer technology. Only authorised users are able to enter or edit data. Changes to data are logged with a computerised timestamp in an audit trail. All data will be pseudonymised. To guarantee high data quality, data validation rules will be defined in a separate data validation plan. Completeness, validity and plausibility of data will be checked in time of data entry (edit checks) and using validating programmes, which will generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or by a designated subinvestigator. The investigator or the designated representatives are obliged to clarify or explain queries. If no further corrections are to be made in the database, eCRF data will be locked. Data will finally be downloaded and used for statistical analysis. All data management procedures will be conducted according to written defined standard operating procedures that guarantee an efficient conduct complying with good clinical practice (GCP). At the end of the trial, the data will be transformed into different data formats (eg, csv-files) for archiving.

Methods for minimising bias

The study protocol has been drafted in adherence to SPIRIT (Standard Protocol Items for Randomized Trials) statement (online supplemental file 2).[35] To reduce performance bias, the patients will be blinded for all endpoints but HRQol and safety issues that would need to be communicated outside of the study due to ethical reasons. By design, the operating surgeons cannot be blinded to usability endpoints. However, they will not be involved in data contribution of any endpoint after the operation. Data collectors, outcome assessors and data

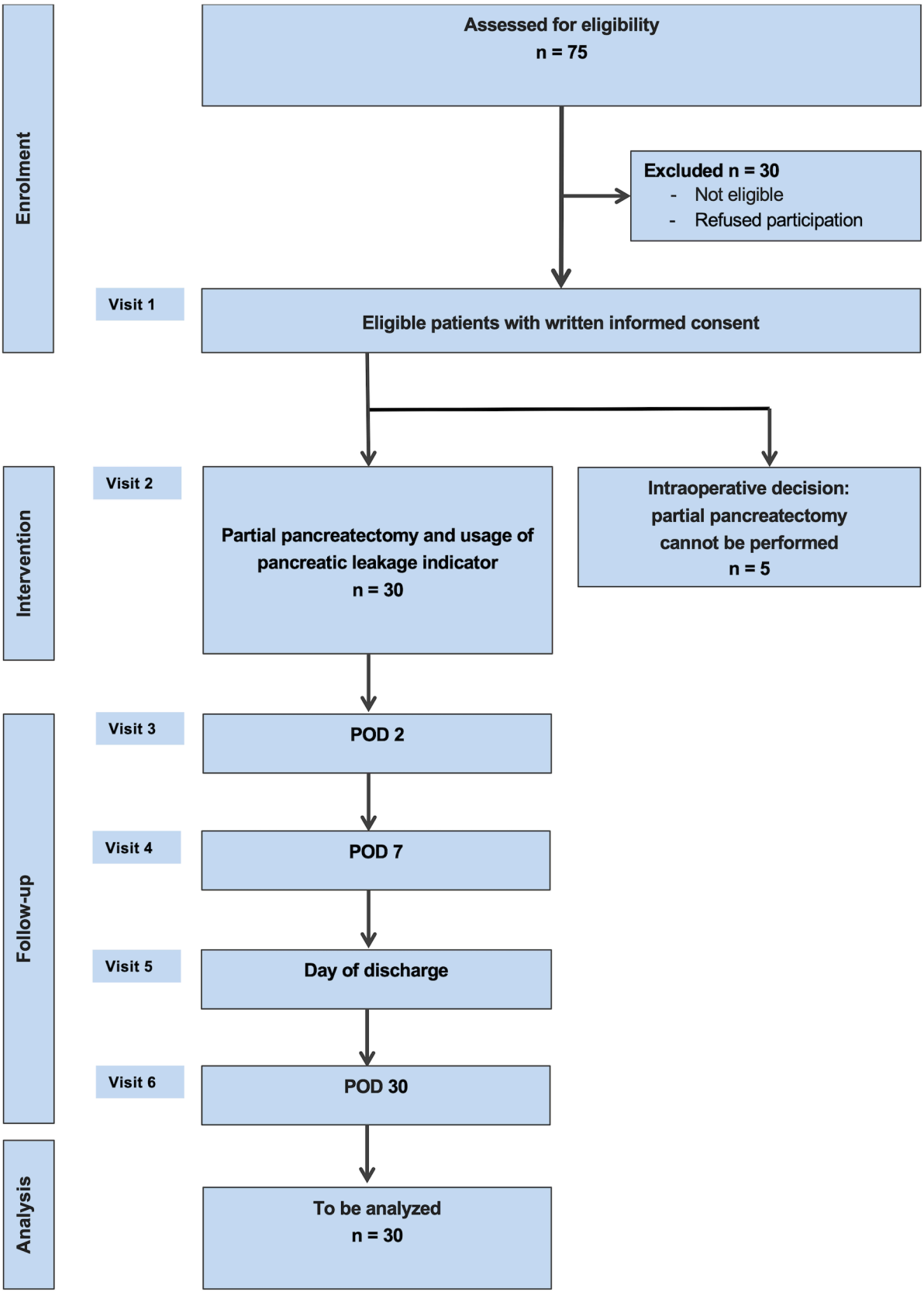

Figure 2 Flow chart of the visualisation of pancreatic leakage (ViP) trial. POD, postoperative day.

analysts will not be blinded, but endpoints are assumed to be robust against their unconscious or intentional influence and therefore detection bias can be avoided.[36]

To avoid the risk of selective reporting, the trial protocol is hereby fully published. The patient flow and the CONSORT (Consolidated Standards of Reporting Trials)

flow chart will be reported with the final analysis. The number of patients screened, included and analysed will be reported, and differences will be explained.

ETHICS AND DISSEMINATION

Study registration, ethics and consent

This trial protocol was approved by the ethics committee of the University of Heidelberg (Medizinische Fakultät Heidelberg, S-043/2022, 4 February 2022). It was registered at the German clinical trial register (DRKS, DRKS00027559, 4 March 2022) before inclusion of the first patient. The ethics committee will be informed of all subsequent protocol amendments in order to determine whether formal approval needs to be sought and whether the informed consent document should also be revised. The study is designed according to the Medical Association's professional code (Berufsordnung der Landesärztekammer Baden-Württemberg) §15 (non-AMG/non-MPG trials). It will be conducted at the Clinical Trial Centre (KSC) of the Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital and the principal investigator will ensure that the implementation will take place in the context of GCP (ICH E6) and in accordance with the Declaration of Helsinki (latest amendment Fortaleza, Brazil, October 2013). All patients will be informed orally. Study aims, consequences and possible risks and benefits will be exposed in detail. It is the responsibility of the study physician to explain patients their duties within the trial and it will be emphasised that participation is voluntary and that the patient is allowed to withdraw further participation in the trial at any time without giving reasons. This will not prejudice the patient's subsequent care. In this case, patients will be asked whether the data recorded up to that date may be used in the analysis of the trial or if it should be discarded. The written informed consent form will be signed and personally dated by the patient after sufficient time to decide on participation (online supplemental file 3). Data collection is performed by the KSC. Statistical analysis will be performed independently by the Institute of Medical Biometry of Heidelberg University Hospital.

Confidentiality

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). Trial-specific documents will be stored in accordance with local data protection law/ICH-GCP Guidelines and will be handled in strictest confidence. For protection of these data, organisational procedures are implemented to prevent distribution of data to unauthorised persons. Original patient data will be pseudonymised immediately before data management and recording. The trial site will maintain a personal subject identification list to enable records to be identified. Third parties have no access to original documents. At the end of the study, all patient data will be anonymised, and the sponsor Magle Chemoswed will receive a data copy including case report forms and raw technical data but excluding any personal patient information. This data copy will be exclusively used for device development and manufacturing as well as for marketing purposes. All data collected during the study will be kept on file for 10 years after completion of the trial.

Access to data

Original data access will be restricted to electronic database manager (MW), study project manager (TP, TH, RK) and study nurses, scientific physicians and a medical doctoral student (FER), all employees of the KSC.

Benefits and risks of trial intervention

All patients receive state-of-the art pancreatic surgery. The study benefit for the patient is the potentially effective indication of biochemical leakage of pancreatic enzymes during surgery, enabling targeted leak closure and prevent POPF development. A risk might be an allergic reaction to one of the SmartPAN components. This risk is estimated to be very low and does not exceed the risk of any allergic reaction to other biomaterials routinely applied intracorporally, i.e., haemostatic glue.[37–40] During product development biocompatibility and toxicity evaluations were conducted according to the international standard guideline (ISO 10993-1:2009.-06[41]; ISO 10993-12018: 2018-08[42]). Degradable starch microspheres are routinely used as haemostatic (Arista by BD, NJ, USA) and embolic agents (EmboCept S by PharmaCept, Berlin, Germany or EmboLog S by Serumwerk Bernburg, Germany). Pharmacokinetic measurements demonstrated that BTB was not detectable in abdominal drainage 2 days after surgery and it could not be detected in the bloodstream.[27] Overall, the components of SmartPAN are either biocompatible or quickly neutralised by dilution and drainage. Usage of SmartPAN in this study is fully aligned to its field of application according to CE-approved market-registration. The ViP-trial will be closely monitored to ensure the identification, documentation and analysis of potential major complications and compliance with the protocol.

Dissemination policy

After completion of the trial, the data obtained will be analysed according to this protocol and published in a peer-reviewed journal. Furthermore, dissemination will be carried out via online media in lay language to ensure accessibility to any healthcare professional or member of the public. The study protocol is available on request. An anonymised minimal data set laying out the results of the trial will be made available on publication of the final results as a supplement in line with data protection rules. The statistical analysis plan will be available on request after publication of the final results.

DISCUSSION

Despite numerous attempts to reduce POPF rates, it is still a frequent and dangerous complication after pancreatic surgery.[7] Since decades POPF has been counted most often among the causes of problems and death.[43] Recently, a root cause analysis has highlighted the typical complication-sequence pattern, which runs from POPF over subsequent complications such as postpancreatectomy haemorrhage[8] or sepsis and following reoperation, eventually to death.[44] Accordingly, there is an urgent need for further innovation in order to lower the risk of clinically relevant POPF. Development of POPF has been attributed to hospital/surgeon-related and to patient-related causes.[45] Mechanisms to control the first group have undergone constant optimization.[1 2 4] Mitigation of the latter group has been limited mainly to patient selection, which from a certain point has limits again. A major patient-related factor which is difficult to predict is the intraoperative nature of the pancreatic gland. Texture of the pancreatic parenchyma and anatomy of pancreatic ducts, two crucial determinants of POPF development,[45] often cannot be ascertained without doubt or auxiliary devices. The development of an indicator of pancreatic leakage that mitigates POPF development by targeted closure or precise drain placement already during surgery is promising. In 1998, the benefit of red litmus paper to visualise alkali pancreatic fluid on the resection margin of human pancreas was explored.[20] However, this method was too crude to be clinically useful. More recent studies relied on a fluorescent chymotrypsin probe activated by enzymes present in pancreatic fluid.[18 19 21] At least their method was successful to visualise pancreatic leaks intraoperatively, but its costs and effort were too high to implement the technique into routine clinical usage. Finally, a Förster resonance energy transfer heat-shock protein probe was developed,[17] but this technique requires specialist equipment not available in most operating theatres. SmartPAN is simple for intraoperative use and provides clear, localised and rapid responses to identify leakage sites related to POPF pathogenesis. Previous studies have proven effective SmartPAN-driven closure of the pancreatic remnant and adoption of appropriate postoperative management in order to reduce the risk of POPF.[26] SmartPAN visualises leakage of alkali pancreatic fluid via colour change of its active component the pH-indicator BTB. In a randomised preclinical trial indicator reaction has been shown to be consistent over a 1 week timeframe.[26] SmartPAN aims to reduce the incidence and severity of POPF which in turn could decrease the rate of postoperative major complications, prolonged hospital-stay and mortality. ViP is the first in-human clinical trial to collect data on the safety and usability of the SmartPAN indicator after preclinical stage 0 has been passed. According to market approval, this PMCF study will evaluate clinical data from the use of SmartPAN in humans within its intended purpose. Exploration of device application in all variants of partial pancreatectomy has been chosen to conclude optimal patient selection for subsequential trials. Additionally, SmartPAN needs careful confirmation of its usability and safety to medical staff and patients in order to introduce this new device to clinical routine successfully. Limitation of the trial is its single-arm single-centre exploratory design. Nevertheless, it generates the conditions of a following exploratory study focused on device performance in the optimal target population. Together these explorations will provide the basis for a high-quality randomised controlled interventional multicentre trial that will investigate the efficacy of the indicator. To this end, several aspects need to be elucidated in our exploratory trial: (1) it is unclear whether and how patients planned for partial pancreatic resection are willing to undergo inclusion to this trial. (2) The results and subgroup analyses from our exploratory trial will help to define the target population of future trials. (3) high-quality data will be collected in our trial to enable sound sample size calculation. Future trials will answer the question of whether the intraoperative visualisation of a potential leakage will lead to clinical superiority in terms of a lower overall morbidity. And they will indicate whether and in which patient SmartPAN should be used within clinical routine.

Author affiliations
[1]Department of General, Visceral, and Transplantation Surgery, Heidelberg University Hospital, Heidelberg, Germany
[2]Study Center of the German Society of Surgery (SDGC), Heidelberg University, Heidelberg, Germany
[3]Magle Chemoswed AB, Malmö, Sweden
[4]Institute of Medical Biometry and Informatics, Heidelberg University Hospital, Heidelberg, Germany
[5]Institute of Forensic and Traffic Medicine, Heidelberg University Hospital, Heidelberg, Germany
[6]Department of Anesthesiology, Heidelberg University Hospital, Heidelberg, Germany
[7]Department of Surgery, Cantonal Hospital Thurgau, Frauenfeld, Switzerland

Twitter Thomas M Pausch @PauschThomas, Martin Wagner @martinwagnerHD, Jan Larmann @JanLarmann, Pascal Probst @ProbstPascal and Rosa Klotz @rosa_klotz

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Contributors TMP, IR, MW, AS, ST, JL, PP, TH and RK are responsible for the study design, definition of endpoints and preparation of the protocol. BG is responsible for preparation of the protocol and its publication. TH provided a clinical perspective as an expert in the field. MB provided expertise in the conduct of toxicological studies. MH, FER and FP provided support with protocol publication. Furthermore, all coauthors revised and approved the final manuscript critically.

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Competing interests TMP reports financial support provided by Heidelberger Stiftung Chirurgie. BG reports a relationship with Magle Chemoswed that includes employment. TMP and TH have patent Body Fluid Leakage Detection Aqueous Composition (Pausch T, Hackert T, Johansson H, et al. European Patent Office, Germany. 2018) licensed to Magle Chemoswed Holding AB and University of Heidelberg.

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 Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Thomas M Pausch http://orcid.org/0000-0001-6145-3263
Jan Larmann http://orcid.org/0000-0003-3365-4572
Pascal Probst http://orcid.org/0000-0002-0895-4015

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Supplementary file 1: Indicator usability score assessment

The following questions addressing six dimensions will be assessed:

Experience

1. How many pancreatic resections have you done so far in your career as a responsible surgeon?
   (<25/25-75/>75)
2. In how many procedures/surgeries have you used the SmartPAN device?
   (0/1/2/>2)

Ease of use

3. SmartPAN was easy to remove from its package.
   (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
4. SmartPAN was easy to use.
   (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
   If disagree/strongly disagree, please specify:
5. It was easy to apply SmartPAN in a homogenous layer.
   (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
   If disagree/strongly disagree, please specify:
6. A complete removal of the indicator from the abdominal cavity was achieved.
   (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
   If disagree/strongly disagree, please specify:

Usefulness

7. Was there a color change?
   (yes/no)
   If a color change (from orange to blue) occurred:
   a) How fast did the color change occur?
      (<30 sec/30s-3min/>3min)
   b) How many areas of color change appeared?
      (1/2/≥3)
   c) How big was the overall diameter which presented a color change?
      (<2mm/2-9mm/>9mm)
   d) The color change was precise (not blurry).
      (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
   e) Durability of color change was appropriate for surgical use (over minutes).
      (Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)
   f) How many extra stiches did you apply after color change?
      (0/1/>2)

g) Did you re-apply SmartPAN after targeted closure?

(Yes/No)

- If yes, did it still indicate a leakage?

  (Yes/No)

- Did you do a second round of targeted closure?

  (Yes/No)

- If yes, how many stiches?

8. SmartPAN is useful for my work.

(Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)

Ease of learning

9. I learned how to use SmartPAN quickly and easily.

(Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree).

Intention to use

10. I would like to use SmartPAN frequently.

(Strongly disagree/Disagree/Neither agree nor disagree/Agree/Strongly agree)

Safety

11. Were there any intraoperative adverse events associated with the use of the product?

(Yes/No)

If an intraoperative adverse event occurred, name event:

Reporting checklist for protocol of "Intraoperative Visualization of Pancreatic Leakage (ViP) – Study Protocol for an IDEAL Stage I Post Market Clinical Study"

Based on the SPIRIT guidelines.

Section/item	ItemNo	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	Suppl.
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact	#5b	Name and contact information for the trial sponsor	12

information			
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	12
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)	10
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	5
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)	5
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	5

		be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5, 6
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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5, 6
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 of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7, Table 1
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)	7, 8, Table 2
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	8
Recruitment	#15	Strategies for achieving adequate participant	7, 8, 9

		enrolment to reach target sample size	
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	n/a
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	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
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	n/a
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,	6, 7, 8, Table 1, Table2

		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
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	n/a
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	9
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	8, 9
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
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)	9, 10, 11
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	n/a
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	n/a

		the trial	
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	8, 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9, 10
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)	9, 10
Consent or assent	#10, 26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12, 13
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	10

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	n/a
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	10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11, 12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl.
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	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

UNIVERSITÄTS
KLINIKUM
HEIDELBERG

Universitätsklinikum Heidelberg | Chirurgische Klinik | Im Neuenheimer Feld 420 | 69120 Heidelberg

Primary Investigator
Prof. Dr. Th. Hackert
Leitender Oberarzt
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 420
69120 Heidelberg
Tel. 06221-56 5150

Trial Coordinator
Dr. med. Thomas Pausch
Facharzt für Chirurgie
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 420
69120 Heidelberg
Tel. 06221-56 5150

Chirurgische Klinik

Prof. Dr. M. W. Büchler
Geschäftsführender Direktor
Im Neuenheimer Feld 420
69120 Heidelberg

Patient Information

ViP-Trial

Intraoperative Pancreatic Leakage Indicator – Post Market Confirmatory Study (PMCF, IDEAL Stage I)

Dear Patient,

we invite you to participate in a clinical study. Please take a moment to learn about the ViP trial being conducted at our hospital. This is intended to confirm the safety and effectiveness of SmartPAN®, an indicator for the intra-operative visualization of pancreatic leaks. The verbal information about the study will take about 20 minutes.

Please read this information carefully so that you can decide whether or not to participate in the trial. Your study doctor will discuss the details of the trial with you and answer your questions. You will then be given sufficient time to decide whether to participate. If you would like to participate in the trial, we ask that you sign the attached consent form, confirming that you fully understand the information provided and that you agree to participate in this trial. The trial presented here was developed by the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital and is also being carried out here. The overall head of the trial is Prof. Dr. medical Thilo Hackert. In accordance with medical professional law, advice was given by the ethics committee of the medical faculty of the University of Heidelberg. In total, it is planned to include 35 patients at our hospital in this trial.

UK HD

Why is this trial being conducted (background and purpose)?

You have been diagnosed with a disease of the pancreas and the treatment planned is surgical removal (resection) of the altered tissue. The doctor treating you will provide you with detailed information about the planned operation.
The most critical complication after an operation on the pancreas is the postoperative pancreatic fistula. Postoperative pancreatic fistula occurs when pancreatic fluid leaks from the remnant of the pancreas, which can result in inflammation, bleeding, and prolonged hospitalization. However, the pancreatic fluid is not visible to the naked eye during the operation. A color indicator is used to make leaks visible during the operation. As a result, the closure suture on the pancreas stump can be checked and, if necessary, corrected during the operation.
The aim of this trial is to continuously confirm the existing data on the usability, reliability and security of SmartPAN® with further information, as required by law.

What if I don't want to take part in the trial (voluntarily)?

Your participation in this trial is voluntary. You will only be included in this study if you have given your written consent. If you do not want to take part in the trial, you will of course not suffer any disadvantages in terms of further treatment. The current standard therapy at our clinic does not provide for the use of SmartPAN® or any other indicator during the operation. The surgeon will inform you about this and discuss the treatment with you.

Which methods are used and examined as part of the trial?

The SmartPAN® indicator is a medical product that was developed in cooperation with the Swedish company Magle Chemoswed and is approved for use in humans. It contains biodegradable starch beads, phosphate buffers and bromothymol blue, which are also routinely used in humans..

What are the benefits and risks of participating in the trial?

All patients are operated according to the latest surgical knowledge. A possible advantage is that the surgeon can already react to the leakage of pancreatic fluid during the operation and thus has the chance to reduce the risk of the occurrence and the complications of a pancreatic fistula. This would make the operation safer overall for the patient. Extensive safety data are available for the components of SmartPAN®, as they are known from other routine applications. They are compatible with the human body (biocompatible) or are quickly neutralized by dilution and drainage.

However, there is a very small potential risk of an allergic reaction to any component of SmartPAN®. It is no greater than the risk of an allergic reaction to other biomaterials routinely used in medicine.

The use of SmartPAN® in this study corresponds exclusively to the area of application according to the approval.

In addition to the scheduled routine blood sampling during the operation, 8ml of blood will be drawn from the central venous catheter for study purposes. However, this only poses a minimal risk.

Intervention in trial participants

Pancreas surgery is performed according to clinical standards. Once the remnant of the pancreas has been occluded, the SmartPAN® Pancreatic Leakage Indicator is applied using a standardized procedure in accordance with the product's Instructions for Use (IFU). The surgical site is then irrigated and the fluid is aspirated and, if necessary, drained to avoid accumulation of the product in the abdominal cavity. If a pancreatic leak becomes visible after application of the indicator, the surgeon can place additional sutures to close the leak and reapply SmartPAN® to confirm the seal. Fifteen minutes after the application, an 8ml blood sample is taken for study purposes and a sample of the fluid is taken from the abdominal cavity at the end of the procedure. If the surgeon places drains to drain fluid from the abdominal cavity, the drain fluid is examined for pancreatic enzymes and bromothymol blue on the second day after the operation. On that day, another 8ml of blood will be taken for study purposes. A total of 16ml of blood is taken.

What alternative therapy options are there?

The alternative therapy option is the current standard of care. The current standard of care does not include the use of an indicator to detect pancreatic leakage after pancreatic resection.

How is the trial going on?

Trial visits: A few days before the operation, after your written consent to participate in the trial, the inclusion and exclusion criteria will be checked and data on your age, height and weight as well as your medical history will be collected. This survey will take approximately 10 minutes. At the beginning of the trial and 30 days after the operation, you will be asked to answer a questionnaire with questions about your condition. Each will take about 10 minutes.

During the 30-day follow-up observation, all data relevant to answering the question about the course of your recovery and any complications that may arise are documented. Employees of the study team will visit you during your inpatient stay on the 2nd, 7th and 30th postoperative day after the operation (and, if necessary, on the day of discharge) or contact you by phone to personally check on your condition and the postoperative course to ask. The rounds and phone calls will last a maximum of 10 minutes. In order to carry out the study successfully, we depend on your active cooperation and therefore ask you to regularly take part in the follow-up visits.

This not only serves to record the trial data more precisely, but also allows precise aftercare and optimal care for you. Please inform your supervising study staff about any complications during the course.

How is further treatment carried out?

The further treatment after the operation (also after the end of your participation in the trial) takes place according to the specifications of your doctor and the therapy standards.

Who organizes and finances the trial?

The ViP trial is being conducted by the Department of General, Visceral and Transplantation Surgery at Heidelberg University Hospital. Magle Chemoswed AB, Agneslundsvagen 27
212 15 Malmö, Sweden funded this trial.

What if I no longer want to participate in the trial at a later date?

You can revoke your consent at any time in writing or verbally without giving reasons and without incurring any disadvantages. If you wish to revoke your consent, please contact the trial management or the study staff supervising you. In the event of a revocation, you can decide whether the data collected from you for the trial should be deleted or may continue to be used for the purposes of the trial.

Even if you initially agree to further use, you can still change your mind later and request the deletion of the data. Please also contact the director of the trial or the staff treating you.

Please note that data that has already been included in scientific evaluations or data that has already been anonymized* can no longer be deleted at your request.

** "Anonymisation" is the changing of personal data in such a way that the person concerned can no longer be identified or can only be identified with a disproportionately large amount of time and money.*

Which data is collected and how is the data protected (data protection)?

Medical confidentiality and data protection regulations are observed. During the trial, medical findings and/or personal information will be collected from you and recorded in your personal file and/or stored electronically at the study center. The legal basis for the collection and processing of your data is your voluntary consent in accordance with the EU General Data Protection Regulation (EU-GDPR).
The data important for the trial are also stored in pseudonymised form**, evaluated and passed on to the trial management and data management (Prof. Dr. Th. Hackert and Institute for Medical Biometry (IMBI) Heidelberg).

***Pseudonymisation is the replacement of the name and other identification features with an identifier for the purpose of excluding or making it significantly more difficult to identify the person concerned (§3 Para. 6a BDSG).*

The trial management will take all reasonable steps to ensure the protection of your data in accordance with European Union data protection standards. The data is secured against unauthorized access.
The data collected during the study will be stored for 10 years after the end of the trial and then destroyed.
The data will be used for the stated purposes of this trial (see "Why is this study being conducted?") and possibly also for further research in the field of pancreatic surgery. You can restrict further processing beyond the study purposes.
You have the right to request information from the person responsible (see below) about the personal data stored about you (Article 15 GDPR). You can also request the correction of inaccurate data (Art. 16 GDPR) and the deletion (Art. 17 GDPR) of the data or the restriction of its processing (Art. 4 No. 3 and Art. 18 GDPR). You also have the right to data portability (Art. 20 GDPR). This means that the data will be made available to you in a machine-readable format.

The person responsible for the trial-related collection of personal data is:
Prof. Dr. Th. Hackert
Phone: +49 6221 56 5150
Email: thilo.hackert@med.uni-heidelberg.de

If you have any concerns about data processing and compliance with data protection requirements, you can contact the following data protection officer at the facility:
Data Protection Officer of the Heidelberg University Hospital
In Neuenheimer Feld 420
69120 Heidelberg
Datenschutz@med.uni-heidelberg.de

In the event of unlawful data processing, you have the right to complain to the following supervisory authority:
The state commissioner for data protection and freedom of information in Baden-Württemberg
PO Box 10 29 32, 70025 Stuttgart
Koenigstrasse 10a, 70173 Stuttgart
Phone: 0711/61 55 41 – 0
Fax: 0711/61 55 41 – 15
Email: poststelle@lfdi.bwl.de
Internet: http://www.baden-wuerttemberg.datenschutz.de

What happens to the results of the trial?

Ihre Daten werden in pseudonymisierter Form analysiert, in zusammengefasster Form publiziert und somit für andere Ärzte und zukünftige Patienten nutzbar gemacht.
Die von Ihnen zur Verfügung gestellten oder im Rahmen der Studie erhobenen Daten werden primär für die in dieser Informationsschrift dargelegten Fragestellungen verwendet. In Zukunft können jedoch weitere Untersuchungen mit diesen Daten erforderlich werden, die im Rahmen anderer Forschungsvorhaben behandelt werden. Die genauen Fragestellungen können jedoch zum derzeitigen Zeitpunkt noch nicht konkret benannt werden. Der Forschungszweck wäre jedoch auf die Pankreaschirurgie begrenzt. Diese künftigen Forschungsvorhaben werden von der jeweils zuständigen Ethikkommission separat beraten. Eine erneute Aufklärung und Einwilligung Ihrerseits wird nicht erfolgen.

New insights

The study doctor will inform you of any new findings that may affect the usefulness or safety of the study and thus your consent to participate in the study.

Do I incur any costs as a result of participating? Do I receive an expense allowance?
Participation in the trial is free of charge for you. However, you will not receive any expense allowance.

Do you have any further questions?

If you have any further questions about your illness, the surgical procedures used or the course of the trial, do not hesitate to ask your doctor. (S)He will be happy to answer these questions in detail.

Your study doctor:

Name: _____

Trial coordinator:
Dr. med. Thomas Pausch
Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 420, 69120 Heidelberg
Tel.: 06221/56- 5150

Further information on the study as well as information about the results and the outcome of the study can be obtained from the study center:

Clinical Study Center KSC

Department of General, Visceral and Transplantation Surgery Heidelberg University Hospital, Im Neuenheimer Feld 420, 69120 Heidelberg

ksc@med.uni-heidelberg.de, Tel.: 06221/56-36209

We thank you for your support.

One copy of this document is intended to remain with you, one copy will remain in the hospital.

Primary Investigator
Prof. Dr. Th. Hackert
Leitender Oberarzt
Klinik für Allgemein-, Viszeral-
und Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 420
69120 Heidelberg
Tel. 06221-56 5150

Trial coordinator
Dr. med. Thomas Pausch
Facharzt für Chirurgie
Klinik für Allgemein-, Viszeral-
und Transplantationschirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 420
69120 Heidelberg
Tel. 06221-56 5150

Declaration of Consent

ViP-Trial

Intraoperative Pancreatic Leakage Indicator – Post Market Confirmatory Study (PMCF, IDEAL Stage I)

I was informed about the type, scope and importance of this clinical study in a detailed explanation. Among other things, Study objective and study duration, study-related requirements and possible risks in the context of study participation are discussed. I have received, read and understood the patient information and a copy of the declaration of consent. In this context, existing questions were discussed and answered.

The following questions / other aspects were also discussed:

_____

_____

_____

_____

_____

No issues were discussed ☐

I am aware that this trial primarily serves to expand medical knowledge and may not bring any personal benefit to me.

I voluntarily agree to participate in the above trial. I had enough time to make my decision. I know that I can revoke my consent at any time without giving reasons and without any disadvantages for my further medical care.

Data protection

I am aware that personal data, in particular medical findings about me, are to be collected, stored and evaluated in this clinical trial. The data is processed in accordance with legal provisions and requires the following declaration of consent in accordance with Article 6 (1) (a) of the General Data Protection Regulation:

I have been informed about this and I voluntarily agree that my data collected in the trial, in particular information about my health***, can be recorded in pseudonymised form for the purposes described in the information sheet, evaluated and, if necessary, also passed on in pseudonymised form, only to countries that are subject to the data protection regulations of the European Union. Third parties do not have access to personal documents. My name will also not be mentioned when the results of the trial are published.

The personal data will be anonymised as soon as this is possible for the research purpose. The data will be kept for 10 years after graduation. Thereafter, all personal data will be deleted, provided that there are no legal, statutory or contractual retention periods to the contrary at this point in time.

The disease data collected as part of this study are documented on documentation sheets in paper form and on electronic data carriers and passed on pseudonymised for scientific evaluation to:

- Magle Chemoswed AB, Agneslundsvägen 27, 212 15 Malmö, Schweden.
- Dr. med. Thomas Pausch/Dr. med. Martin Wagner, Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Universitätsklinikum Heidelberg (Studienkoordinator, Datenmanagement).
- Institut für Medizinische Biometrie, Universitätsklinikum Heidelberg (Biometrie).

In addition, I agree that authorized representatives of the trial director, so-called monitors, who are sworn to secrecy, may inspect my personal data available from the study doctor, in particular my health data, insofar as this is necessary for checking the proper implementation of the study is necessary. For this measure, I release the study doctor from medical confidentiality.

I am aware that this consent can be revoked at any time in writing or verbally without giving reasons and without any disadvantages for me. This does not affect the lawfulness of the data processing that took place until the revocation. In this case, I can decide whether the data collected from me should be deleted or may continue to be used for the purposes of the trial.

I would like to limit the use of my data for other/future research purposes as follows:

_____

*** Pursuant to Art. 9 Para. 1 GDPR, health data is personal data of a special category, the processing of which must be expressly consented to by the trial participant.

Patient's first/last name (in block capitals)	Date of birth

Signature of the patient	Date (to be entered by the patient)

Informing and consent receiving person

I informed the patient about the aim and procedure of the trial as well as the risks during a conversation. I gave the patient a copy of the patient information and the declaration of consent.

Name of study doctor (in block capitals)	Date (to be entered by the study doctor)	Signature of the study doctor